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INSTITUTO DE MEDICINA TROPICAL

PROCEEDINGS OF THE SIXTH INTERNATIONAL CONGRESSES ON TROPICAL MEDICINE AND MALARIA

Lisbon, September 5-13, 1958

VOLUME VII

LISBON, PORTUGAL

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Anais do Instituto de Medicina Tropical
Vol. 16, Suppl. No. 11, 1959

EMP. TIP. CASA PORTUGUESA — LISBOA

DIVISION B

MALARIA

SECTION 1

PARASITOLOGY

1ST SESSION: *Tuesday, September 9th, 3:00 to 4:30 p.m. Room D*

The meeting was held under the Chairmanship of Dr. Henry E. Shortt and Dr. N. R. Swellengrebel.

The Rapporteur was Dr. Clay G. Huff and the Secretary was Dr. José S. Queirós.

The following papers were presented and discussed.

TIME-LAPSE MOVING PICTURES OF THE DEVELOPMENT OF THE EXOERYTHROCYTIC STAGES OF AVIAN MALARIA IN TISSUE CULTURE

CLAY G. HUFF, ALAN C. PIPKIN, DINNIEMAUD V. JENSEN,
and A. BURNS WEATHERSBY

ABSTRACT

The complete exoerythrocytic development of *Plasmodium gallinaceum* and *P. fallax* is shown as it occurs in primary tissue cultures made from the liver of chick embryos. The nature of the motion of free merozoites, their penetration into host cells, the growth of the schizont and the production of new merozoites are portrayed. In addition, some sequences of nuclear division in both the host cell and parasite and of phagocytosis of parasites are included. The exposures were made at the rate of 16 per minute and by means of phase contrast optics. At a projection speed of 16 frames per second the viewing action is 60 times the speed of movement. All sequences were taken at this speed unless otherwise noted in the legends.

PLASMODIUM GALLINACEUM IN TISSUE CULTURES: RESULTS OBTAINED DURING 4 YEARS OF UNINTERRUPTED CULTIVATION OF THE PARASITE *IN VITRO*

H. Meyer and M. de Oliveira Musacchio

When in 1947 we began the cultivation of *Plasmodium gallinaceum* in tissue cultures we used the exoerythrocytic form of the parasite to start with. This form can be obtained easily, and in great quantities from chicks with blood infection which had been treated with quinine. We explanted fragments of the brains of such animals into Carrel flasks, together and in contact with fresh, normal embryonic brain or spleen. After about 10 days of cultivation the cultures were transferred to hanging drops which allow the observation of the living culture with the highest microscopical magnifications. We could see then *in vivo* the parasite within the cells in all the different stages of its cycle and confirm the findings of Huff and Coulston[1] who described the various phases of the cycle in young chicks which had been inoculated with sporozoites.

In continuous observation over several days it has been possible to see small schizontes become larger and develop into rosacea formations which represent the end of the cycle. At this stage, at a certain moment, the rosaceas break up, the host cell ruptures. and the single merozoites are thrown into the surrounding medium. For a short time they move, apparently by their own activity. Many of them are phagocyted by the cells of the neighbourhood, and begin a new cycle there. Those merozoites which are not phagocyted degenerate soon. It was also seen that the parasites of the original, infected tissue had passed into the normal one, and in this way it had been possible at that time to maintain *Plasm gall.* in tissue cultures for about 4 months. Up to 4 months one parasitized tissue culture was enough to infect and to kill one new-born chick. The animals which were infected by intramuscular inoculation of one parasitized tissue culture had an exoerythrocytic infection first, and later the infection of the blood. And the blood of such chicks, when inoculated into normal chicks, gave for many passages, after an initial blood infection, exoerythrocytic infections in the birds. These observations have been confirmed later by Lewert[1] in the United States, who speaks of an «alteration» of the malaria strain.

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[1] Huff, C., and Coulston.

Nevertheless, the cultivation of the parasite has been difficult and not satisfactory because it did not yield the great masses of parasites as did *Trypanosoma cruzi* or *Toxoplasma* which we had in culture at the same time. *Plasm. gall.* always spread slowly, as Hawking[2] had observed before us, around the initial areas. So we could not sacrify as many cultures for more detailed investigations as would have been necessary.

We obtained better results when we began to cultivate in Roller tubes. This method, advised by Gey and Gey, gives easily great amount of cells, but does not allow microscopical observations with higher magnifications. For these we transferred the cultures to hanging drops, and later back to Roller tubes. We saw then that in the Roller tubes the parasites spread rapidly over the whole culture, and infected the normal cells. It was necessary to add fresh tissues almost every ten days, because the lack of normal unparasitised cells would have meant the loss of the plasmodium which is necessarily an intracellular parasite. In 1954 we were able to publish a paper dealing with the results obtained during one year of cultivation. These results were essentially that it had been possible to maintain *Plasm. gall. in vitro* for one year, and that during that time no changes had been observed in its morphology or in its virulence. Like in the beginning, one tissue culture was enough to infect and to kill a newborn chick, always provoking the exoerythrocytic infection first, and later the infection of the blood.

During the following years we had to interrupt these investigations, in order to get acquainted with the techniques for electron microscopy which we intended to use for further study. But we always kept plasmodium strains in culture. When later we resumed these investigations, we noticed that one strain, which had been in culture for 22 months, showed a very atenuated virulence. The chicks which were inoculated with it, survived, after only a slight infection of the blood, and, apparently, no exoerythrocytic infection at all. This strain, which has the number 837, has been maintained now for more than 4 years uninterruptedly *in vitro,* in tissue cultures of embryonic brain and heart-muscle. Its aspect continues normal, at least as seen with the ordinary optical methods.

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[1] LEWERT, R. — *Amer. J. Hyg.*, 51, 155, 1950.

[2] HAWKING, F. — *Trans. R. Soc. Trop. Med. Hyg.*, 39, 254, 1945.

We tried to use this strain for immunisation against the disease, and in a preliminary test, some chicks were inoculated with it. After the slight blood infection had passed, they were reinoculated with infected blood of malaria chicks. This blood injection killed all the normal chicks which had been inoculated as controls; but all the chicks which had been inoculated with culture material before, survived [1]. These results have to be, and are beeing investigated further and on greater scale. We do not know the reasons for the change in the virulence of the strain 837. It is difficult to believe that the time of cultivation is the only important factor, when for almost one year no change had been observed. Several new strains have been initiated in the meantime which proved virulent up to 10 months so far.

A more detailed comparative study of the morphology of these different strains with the help of the electron microscope might show differences. However, such investigations are still under way, and the first electron micrographs of this study which will be presented here have to be considered as preliminary results only. They give the images of the exoerythrocytic forms in tissue cultures of that weakly virulent strain 837 which has been maintained *in vitro* for more than 4 years now. Whole tissue cultures have been fixed with 2 % osmic acid in buffered solution, embedded in methacrylate, sectioned with a Porter--Blum microtome, and examined with a Philips electron microscope.

DEMONSTRATION

The schizontes show a cytoplasm of low electron density with particles of uncertain form and irregular distribution. The nuclear masses have a higher electron density, are of irregular shape, a membrane is not well defined. The masses seem to go over directly into the cytoplasm. Mitochondria like formations and an endoplasmic reticulum can be seen occasionally.

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[1] MUSACCHIO, M. de Oliveira, e MEYER, H. — *O Hospital,* vol. 53, n.º 3, 1958.

During the beginning of segmentation small double walled spaces appear scattered over the whole body, and in places at the periphery. Also rupture of the cytoplasm is observed; generaly the open space has a convex double walled surface at one side, the other side shows the margin of the retracting membrane. The nuclei are better defined, and near by an oval formation of high electron density can be found which has a fine granular structure. The cytoplasm shows the beginning of a fine more organised granulation of about 250 Å diametre.

When the segmentation is more advanced the open spaces become larger, the nuclei still better defined also the small electron dense oval body. The individualisation of the single units apparently begins at the two poles of the future merozoites. Still the surface membrane is poorly visible. The more the segmentation advances, the more we can devine the future units. The margin of the schizontes cytoplasm becomes very empty now, but shows in some peripheral places a greater electron--density.

The final rosacea shows the parasites in many different positions, and therefore every merozoite is cut in a different plane. All the single units are grouped around one cytoplasmic center piece, the structure of which is very similar to the structure of the cytoplasm of the host cell. There is a double membrane to be seen in some regions, depending on the direction of the cut. The single parasite has a large nucleus and a smaller oval body, of still higher electron-density, at the peripheral pole. Around the nucleus we see a lighter area, structurally empty, compared with the surrounding cytoplasm of the merozoites. In the cytoplasm we see the fine granulation of about 250 Å, and a larger one of about 750 Å. Depending on the direction of the cut the smaller granules show often a quite regular, linear arrangement. So far, we have obtained only very few images of free merozoites where the whole or the greater part of the parasite appears. It seems to be a well organised unit. It is covered by a clear double membrane. At one pole we see a ring-like formation which goes over into a vacuole-like oval space in the body. Behind this we see the nucleus surrounded by the cytoplasm, which has the fine granulation. Larger granules are seen in the upper part of the unit.

THE FINE STRUCTURE OF *PLASMODIUM BERGHEI* [1]

MARIA A. RUDZINSKA and WILLIAM TRAGER
Rockfeller Institute, New York, N. Y.

An electron microscope study of thin sections of rat erythrocytes infected with *Plasmodium berghei* revealed that the parasite is an intracellular phagotroph. It feeds on its host cell in the same way as *P. lophurae*. In addition two new structures not previously found in any other cell were uncovered.

The parasite lies within the host cell, usually a reticulocyte (figs. 1-3). Its body is surrounded by two thin membranes closely adjacent to the cytoplasm of the host (figs. 2-3). The most prominent structures in the majority of sections are oval bodies of the same appearance and density as the cytoplasm of the host (figs. 1-3). Clear evidence as to their origin was found in a number of micrographs showing continuity between these bodies and host cytoplasm (fig. 2). It became obvious that they represent parts of host cytoplasm engulfed into the body of the parasite, and as such may be regarded as food vacuoles. Close to the vacuoles and sometimes connected with them small vesicles are present which contain the pigment hematin (figs. 1-3). It is assumed that the small vesicles are parts of the food vacuole from which they are pinched off, and that digestion of hemoglobin takes place within these vesicles.

In the ground substance of the cytoplasm many dense small granules may be found which represent Palade's small particles containing ribonucleoproteins. The endoplasmic reticulum is composed of oval vesicles and canaliculi. In the cytoplasm two new organelles are present. One is oval in shape and composed of two to six double membranes arranged concentrically (fig. 3). In some electron micrographs continuity between the concentric structure and the double limiting membrane of the body

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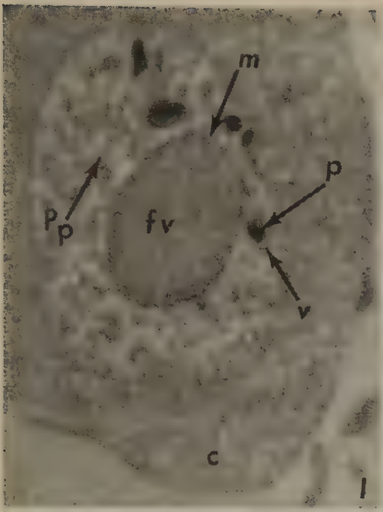
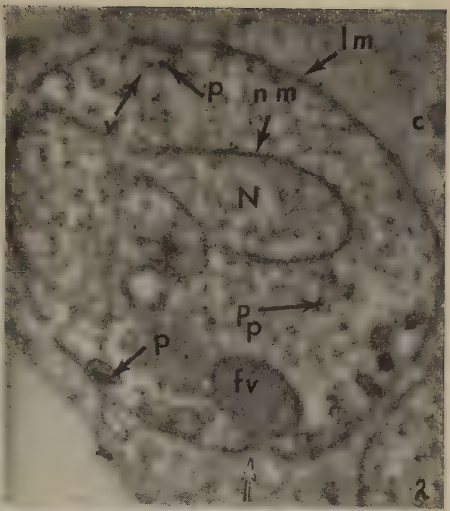
[1] Supported by a grant (E1407) of the National Institute of Allergy and Infectious Diseases, U. S. P. H. S.





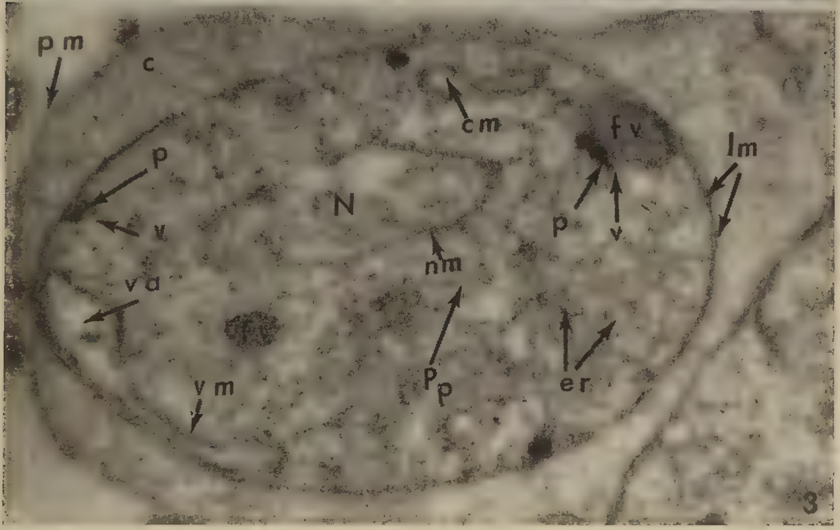


Fig. 1 — Section through young *Plasmodium berghei* inside a reticulocyte. In the center of the body a large food vacuole (fv) surrounded by two membranes (m) may be seen. The matrix of the food vacuole has the same density and structure as the cytoplasm of the host cell (c). Several vesicles (v) containing the pigment hematin (p) are in the vicinity of the food vacuole. The cytoplasm is filled with Palade's particles (Pp). Magnification 37,000.

Fig. 2 — A parasite with a food vacuole (fv) at its late stage of formation, but still connected with the cytoplasm of the host cell (c) at white arrow. The nucleus (N) is large and apears in preparation for division. It is surrounded by a double membrane (nm). Palade's particles (Pp) are scattered in the cytoplasm. A few vesicles (v) containing pigment granules (p) are near the periphery of the cell. A double limiting membrane (lm) surrounds the body of the parasite. Magnification 40,000.

Fig. 3 — *Plasmodium berghei* showing two new organelles. One is composed of concentric double membranes (cm) and the other looks like an elongated vacuole (va) with bulb-like enlargements at its ends. It is surrounded by a double membrane (vm). An elongated nucleus (N) is encased in a double nuclear membrane (nm). Four vesicles (v) with hematin (p) are seen at the periphery of the parasite body, and two seem to be connected with one of the food vacuoles (fv). The cytoplasm contains vesicles of the endoplasmic reticulum (er) and is rich in Palade's particles (Pp). The double limiting membrane (lm) separates distinctly the body of the parasite from the host cytoplasm (c). The latter is surrounded by a single plasm membrane (pm). Magnification 40,000.

was found and also early stages in its formation from the double plasma membrane, leaving no doubt as to its origin. Since no typical mitochondria are present in *P. berghei,* it is assumed that this structure performs mitochondrial functions. The other new organelle appears usually near the periphery of the cell. It is elongated, irregular in shape, with bulb-like enlargements at its ends (fig. 3). It is surrounded by two membranes of the same thickness and density as the double plasma membrane, from which most probably they are formed. The matrix of this organelle is of very low density. Its function is unknown.

The oval, elongate and sometimes irregular nucleus (figs. 2-3) often has a density the same as or lower than that of the cytoplasm. It is surrounded by two thin membranes, the external one tending to fuse with the internal plasma membrane when both are closely approximated.

The host cells, usually reticulocytes contain in their cytoplasm vesicles of endoplasmic reticulum, and of the Golgi apparatus. The mitochondria display the regular structure of mammalian mitochondria and are rich in cristae mitochondriales. In some reticulocytes vacuoles and mitochondria filled with ferritin were found.

TELOSPORIDIA AND THEIR CHROMOSOMES

ARTHUR C. WALTON

In an attempt to determine whether chromosome number or behavior might give further clues to the relationships of various parasitic protozoa, laboratory and library studies have been made of a variety of forms. For the purpose of this report, illustrative materials have been selected from among the Telosporidea and examples from the Haemosporidia, the Coccidia, and the Gregarinida are presented.

The Telosporidea is the only subclass of the subphylum Sporozoa that seems to be a fairly homogeneous group with true taxonomic validity, yet even in this group one finds that relationships are often obscure. Examples from among the Haemosporidia, particularly in the genus *Plasmodium,* gives some useful information. Use of modern staining techniques and observations on living material with the phase microscope have indicated certain groupings within the genus. One group, as was indicated by Wolcott (1957) and substantiated to some degree by observations by Bano (1958) and in my own examinations, is made up of such species as *Plasmodium vivax, P. ovale, P. malariae,* and *P. falciparum* from man, and *P. knowlesi* from monkeys — all having a haploid complement of two chromosomes of unequal size. To this group might be added *P. cynomolgi* (from monkeys) which shows the haploid number of four chromosomes, two of which are larger than the other two. On the basis of the inequality of size expressed here, this form seems more closely allied to the above group, and since there are only two size catagories, may represent a case of polyploidy. The second group of species all seem to have chromosomes of equal size and here again the basic number of chromosomes is two, with one exception of a species with four equally sized chromosomes. In this group one finds forms such as *Plasmodium berghei* (from rodents), *P. lophurae* (from ducks), *P. relictum* (from sparrows), *P. cathemerium* (from canaries), *P. gallinaceum* (from quail), and *P. floridense* (from lizards). According to observations by

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 17-20, 1959

Bano (1958), *Plasmodium inui* from monkeys should be included here since all of the chromosomes are of the same size although four in number. Again this may be a case of polyploidy. This grouping brings together parasites of cold-blooded reptiles, warm-blooded birds, and warm-blooded mammals as opposed to the first group in which all species are from mammals.

On the basis of the above apparent groupings, one might speculate as to which one was the more primitive and which the more advanced. Undifferentiated chromosomes and a wider range of hosts might be regarded as indicative of traces of the pathway along which evolution from earlier geologic times has passed, but the evidence is based on far too few examples. Examination of all of the known species of Plasmodia might well indicate whether such interpretation could be more than mere speculation. Another question of possible interest is the occasional appearance of species with seemingly double the number of chromosomes characteristic of the genus as a whole. One wonders whether it might point to a complex structure of the chromosome that reflects an ancestral condition in which the chromosome number was greater.

When one turns to the Coccidia, one finds relatively few records of chromosome counts, and until checked by the newer methods, one is not too sure of the accuracy of records. The few observations made in our laboratory would tend to indicate that some of the so-called chromosomes were probably not chromatin in make-up, and possibly the counts recorded have been too high. The Adeleidae, as represented by the myriapod parasites *Adeleina cryptocerci* (? 10 chromosomes) and *A. deronis* (? 12 chromosomes), might be considered as a primitive family within the suborder if the dictum of numerous, undifferentiated chromosomes means a clear reflection of ancestral conditions, which is showing some specialization in the genus *Klossia* where we find *K. loossi* (from a mollusk) with only four chromosomes. On this same line of thinking, the Eimeriidae, as represented by *Eimeria tenella, E. bovis,* and *Isospora felis* with only two somewhat differentiated chromosomes should be regarded as still more highly specialized forms. It might be noted here that the forms from the warm-blooded hosts tend to have a fewer number of chromosomes than do the species from invertebrate hosts. If, as many investigators have stated, the Coccidia have evolved from a flagellate ancestor, they have deviated considerably from the flagellate pattern. No real relationship between the Eimeriidae and the

Adeleidae can be traced if one depends solely upon the evidence present in terms of chromosome number or behavior, and it would be questionable to state that within the Adeleidae the genus *Adeleina* was ancestral to the genus *Klossia* simply because there was a reduction in chromosome numbers and the beginning of size differentiation among the chromosomes of *Klossia,* especially in view of the limited number of examples studied.

Among the Gregarines, the Acephalina are represented by records from *Urospora lagidis* (from a pectin) showing 4 chromosomes and from *Zygosoma globosum* (from an echinurid) showing 6 chromosomes. The Cephalina group is represented by records from *Gregarina blattarum* (from a cockroach) showing 3 chromosomes and from *Stylocephalus longicollis* (from a molusk) showing 4 chromosomes. These records are too few in number to be indicative of any necessary taxonomic relationship of the two groups, or even of relationships within a group.

One might speculate that the haemosporidians originated from the blood coccidia (haemogregarines) of invertebrates, later adopted a cold-blooded vertebrate as an alternate host, and eventually became acclimated to an alternating life cycle involving an invertebrate and a warm-blooded vertebrate host. Another series of changes involved periods in the cycle when the organism in its vertebrate host invaded the tissue cells and then later re-entered the blood stream and made use of the erythrocytes as a place for further development before becoming infective for the invertebrate portion of the cycle. During such an evolution a gradual reduction in the numbers of chromosomes and the morphological differentiation between chromosomes may have occurred. It would be pure speculation, however, for the evidence is scanty, but since the few cytological studies that have been carried out do not contradict such postulated steps, further studies should be carried out to ascertain whether additional evidence would clarify the picture one way or another. Studies on groups above the Protozoa have aided materially in clearing up some uncertainties of taxonomic position, and more studies on the various groups of the Protozoa may well be of equal value. Certainly such has been the case among some of the flagellates as well as the studies of Wolcott and of Bano on Plasmodia.

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STAGES OF *IN VITRO* CULTIVATION OF THE MOSQUITO PHASE OF *PLASMODIUM RELICTUM*[1]

Gordon H. Ball and Jowett Chao
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The relationship between a host and an obligatory parasite is one which is coming more and more under scrutiny by experimental methods. A fundamental question in parasitology which must be answered is what particular factor or factors lost by the parasite in the course of its evolution are now supplied by its host so that the parasite has come to be dependent upon the host. In what respect have these relationships become so specialized that one species of host proves to be a good vector of a certain parasite, while in another host species belonging to the same genus, development either does not occur or else goes on very slightly? In the latter case, the host is known as a poor vector.

The various species of mosquito which serve as poor to excellent vectors of malaria parasites offer an opportunity of determining the essential demands of the parasites which are supplied by a particular species of host. The erythrocytic stages as well as the tissue phases of several species of malaria have been cultivated *in vitro*. If the portion of the life history in the mosquito could be grown in culture in media of known composition, then it might be possible by altering the medium either quantitatively or qualitatively, to begin to solve the riddle of host-parasite inter-relationship.

The parasite chosen for these investigations was the avian malaria parasite, *Plasmodium relictum*. The host was *Culex tarsalis*, which has proved in the laboratory to be a very efficient vector, about 90 % of these mosquitoes which bite a host with gametocytes in its blood becoming infected. The parasite can easily be maintained in the laboratory in the common canary as the vertebrate host. In view of the successful cultivation of the erythrocytic stages of *Plasmodium* through more than one asexual generation in a medium made up of known constituents plus normal blood and serum (Anfinsen *et al.*, 1946), media of this nature were used in an attempt to grow the mosquito phase of *P. relictum in vitro* (Ball, 1948, 1954). In addition, a medium of unknown chemical constitution but which had proved successful in growing equine encephalomyelitis virus in association with mosquito tissue (Trager, 1938) was employed. This consisted essentially of glucose, egg digest, inorganic salts and chicken or rabbit plasma. The results of such experiments were the persistence of oocysts *in vitro* for as long as 20 days, but with no visible development, the oocysts remaining apparently normal over this time (Ball, 1947, 1948).

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[1] Aided by grants 1857 and E-87 from the National Institute of Allergy and Infectious Diseases and grant 254 — Univ. of California, Board of Research.

Since insect tissue is notoriously difficult to grow in culture, it was felt that degeneration of associated host tissue might play an important role in the failure of the parasites of the mosquito phase to develop under the same conditions which were suitable for the erythrocytic stages. Consequently, a biochemical study of the vector *Culex tarsalis* was undertaken, with the aim of changing the medium so that it would approximate more closely the environment of the natural host. This involved an investigation of the aminoacids, the inorganic constituents, and the proteins detectable in the whole bodies of *Culex tarsalis* (Clark and Ball, 1952, 1954, 1956). Findings from these studies were used to alter the media tested. In addition, substances known to have high growth potencial, such as chick embryo extract, were also added to the media. The results were: (1) a marked improvement of the condition of the mosquito digestive tract over a considerable length of time in culture, contraction persisting for as long as 5 weeks; and (2) the development of malarial oocysts over a period of 4 to 5 days with a threefold increase in size (Ball, 1954). An incidental finding was the discovery of differences in the aminoacid picture among species of the same genus of *Culex* (Ball and Clark, 1953).

The demonstration by Weathersby (1952) that the oocysts of *P. gallinaceum* could develop *in vivo* free from the mosquito stomach prompted a series of experiments to see if oocysts of *P. relictum* could be cultivated apart from the stomach of the mosquito (Chao, 1955). This procedure would limit the problem to that of cultivating the tissues of one instead of two organisms *in vitro* at the same time. The results (Ball and Chao,

1957) showed that oocysts of *P. relictum* would develop in culture when they were separated from the intact mosquito stomach, but they did not pass beyond the stages reached by oocysts attached to the whole organ.

It has now been found that *in vitro* development will occur for some time if a stomach is removed from a *Culex tarsalis* shortly after the latter has bitten a bird with these stages in its blood. The gametocytes produce gametes, e. g., exflagellation in the case of the microgametocyte. The gametes give rise to ookinetes. When ookinetes develop, mosquito stomachs in the same culture chamber eventually show oocysts which reach a size of 17 μ in 5 days, in some instances doubling in diameter during the last twenty-four hours.

Stomachs of other mosquitoes in which oocysts were no larger than 10 μ in diameter were cultivated with attached oocysts, or else the oocysts were dissected away from the stomachs and grown separately. These increased in diameter for a period of five, and occasionally up to eight days, reaching a maximum diameter about three times that of the oocyst before cultivation. The actual volume increase of the new protoplasm in the oocyst was of course considerable.

If oocysts in which sporozoites are not yet visible, but in which they would be seen *in vitro* 1-2 days latter are subjected to the same cultural conditions, they will develop so that sporozoites appear within them.

Hence, by selecting infected mosquitoes at appropriate times after biting, it is possible to obtain a series, which has developed in culture from gametocytes to oocysts with visible sporozoites internally. In these cases, *in vitro* development proceeds in each culture for 5 days, but at a rate slower than takes place in the body of the mosquito maintained at the same temperature.

Up to the present, no infection has been obtained in clean birds injected with oocysts containing sporozoites which have developed in culture. Indeed, the question has never been satisfactorily settled as to whether sporozoites are normally infective while still within the confines of a mature oocyst.

These investigations have demonstrated that the mosquito phase of the cycle of *Plasmodium relictum* can be cultivated *in vitro* ordinarily attached to the digestive tract of the vector *Culex tarsalis*. However, at least some of the oocyst development can take place apart from any except mere fragments of mosquito tissue.

The problem posed in the introduction of this paper has not yet been satisfactorily solved; namely, cultivation of the mosquito phase of a malaria parasite in a medium of known constitution which substitutes successfully for the normal host. Until this has been accomplished, it seems some what futile to speculate about those essential needs of a parasite which are fulfilled by a particular host. On the other hand, the fact that the complete cycle in the mosquito can be shown to take place *in vitro* indicates that considerable progress has been made in the solution of this problem.

From the experiments performed, the requirements for sucessful cultivation of the mosquito phase of *Plasmodium relictum* are: (1) a medium of considerable complexity, which includes some serum or plasma and possibly a substance of high growth potency such as embryo extract; (2) aeration with a mixture of 5 % CO_2-95 % air; this aeration may be intermittent rather than continuous; (3) a temperature of 22°-25° C; (4) freedom from microbial contaminants or associates. The cultures grow better if they are transferred every 24 or 48 hours to fresh medium, if they are subjected to constant but gentle rocking, and if the developing oocysts are attached to host tissue. No one of this latter set of conditions, however, is absolutely essential. If the development of these stages is to be followed from day-to-day, it is of great value that the structures cultivated be grown in small chambers, such as hanging drops or Carrel flasks or else that they be firmly attached to some substrate such as a piece of a cover slip. Only in this way can the day-to-day progress of the same structure be followed with certainty.

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GENERAL DISCUSSION

Dr. R. S. Bray — 1. I would like to make one comment on what Dr. Walton has told us. It is, I feel, difficult for a malariologist to believe at present that the findings of both Wolcott and Bano are completely compatible as I understand Dr. Walton implies. It is difficult to believe that *P. vivax* and *P. malariae* have two uneven chromosomes and *P. cynomolgi* and *P. inui* have 4 chromosomes, two very short and two very long. I, for one, do not feel that I can accept both these findings as final and I believe some reconciliation through further work is necessary. I have seen in *Plasmodium,* or as I prefer it, *Haemamoeba giganteum* of agamid lizards Wolcott's unequal bodies. In Wolcott's groupings a lizard malaria parasite seems more likely to have equal chromosomes. This increase my suspicion that this question is very far from closed.

2. Several years ago Dr. Meyer was attempting to infect tissue cultures with erythrocytic forms of *P. gallinaceum.* I understand she decided that the infections she obtained at that time were due to circulating exoerythrocytic forms in blood leucocytes. Could she tell us if since that time she has any further success in her endeavours to infect tissue *in vitro* with erythrocytic parasites?

Dr. N. Swellengrebel (Netherlands) — How does Dr. Walton know that in *Plasmodium* he is actually seeing *chromosomes*?

Has Dr. Ball seen the oocysts have their own wall?

Dr. G. H. Ball (U. S. A.) — The studies of Dr. Weathersby have shown that the stomach wall of the mosquito is not necessary for the successful development of the malarial oocysts, since oocysts develop to complete maturity elsewhere in the body of the mosquitoes.

Our own microdissection studies have demonstrated that the oocyst has its own wall development, independent of that of the mosquito tissue. The wall of the oocysts behaves very differently from the tissues of the host. I would be inclined to say the oocyst has its own wall. Dr. Weathersby's results would also support this conclusion.

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2ND SESSION: *Wednesday, September 10th — 9:00 to 10:30 a.m. Room D*

The meeting was held under the chairmanship of Dr. Giulio Raffaele and the Rapporteur was Dr. Clay G. Huff. The Secretary was Dr. José S. Queirós.

The following papers were presented and discussed:

RELAPSES AND IMMUNOLOGICAL COURSE IN PLASMODIUM INFECTIONS

AUGUSTO CORRADETTI
Roma, Italia

When we start to make a comparison of the spontaneous immunological courses of the different Plasmodium infections, we immediately realize that a great deal of variation occurs, and that these variations are conditioned by factors, which chiefly depend on the mode of development of each species of parasite in the respective host.

I wish to recall here some of the most characteristic patterns of the immunological courses occurring in Plasmodium infections[1].

1. *Plasmodium rouxi,* in canaries, after blood inoculation.

Infection lasting the entire life of the host (longest infection observed in personel experiments: more than 773 days. Infection characterized by low parasitaemia, no definite primary attack, no immunity crisis. Infection in previously splenectomized canaries is characterized by shorter incubation, slightly higher parasitaemia (in some occasions progressively higher until death), and shorter length of the host life. Splenectomy

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[1] For details on the subject see my previous papers reported in the bibliography, chiefly that published in 1955 in which are listed and summarized all my papers appeared from 1938 to 1955.

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during infection can produce an increase of the parasite number which can be either transitory or progressive until death.

2. *Plasmodium elongatum* (Conggeshall strain), in canaries, after blood inoculation.

Schizogony in any type of blood and blood-forming cells (chiefly in cells of the red series from mature red cell to haemocytoblast). Parasites occurring in both circulating blood and haemopoietic tissues the entire life of the host. Infection characterized by no definite primary attack and no immunity crisis. High mortality during the first five weeks of infection (longest infection observed in personal experiments: 31 weeks). Some other strains, taken from sparrows captured around Rome, invariably killed the canaries in less than five weeks.

3. *Plasmodium gallinaceum,* in fowls. A) After sporozoite inoculation. Pre-erythrocytic cycle in monocytes and reticular cells, then both exoerythrocytic cycle in R. E. cells and cycle in erythrocytes.

B) After inoculation of brain tissue containing exoerythrocytic forms: Simultaneous attack of both R. E. cells and erythrocytes.

C) After inoculation of erythrocytic forms: Patent infection erythrocytic at the start; then exoerytrocytic parasites appearing suddenly at the 11th day of patent infection, or never appearing (if the erythrocytic attack is suppressed by crisis before the 11th day).

Infections produced in chickens by anyone of the above methods (A, B, and C) are characterized by a transitory exoerythrocytic cycle (lasting less than six weeks), and a cycle in the red cells persisting for the life of the bird.

4. *Plasmodium berghei,* in albino rat, after blood inoculation: Severe infection. In surviving rats the infection ends with an immunity crisis, by which all the parasites are destroyed in less than 50 days after the end of the primary attack (usually much earlier).

A strong state of immunity to re-infection follows, persisting the whole life of the rat, while parasites in the body are absent, as revealed by both splenectomy and subinoculations.

5. *Plasmodium cynomolgi,* in Macacus monkeys. A) After injection of sporozoites: Pre-erythrocytic cycle in epithelial (parenchyma)

cells of the liver. After the first schizogony, red cells are invaded as well as other liver cells. Schizogonic forms in these latter were found in some occasion many months after the sporozoite inoculation (Shortt, Garnham, Bray and collaborators). The course in the blood is characterized by a primary attack ending by crisis, and periods of latency alternating with relapses, until complete recovery occurs (within 3-4 years).

B) After blood inoculation: no production of schizogony in epithelial cells of the liver. Infection purely erythrocytic. Primary attack ending by crisis, and followed by periods of latency alternating with relapses until complete recovery (longest infection in personal observations: 703 days).

Some interesting phenomena can be noted by analizing these selected patterns of Plasmodium infections.

First of all it is evident that the three above noted species of Plasmodia of birds all show an erythrocytic infection persisting for the whole life of the host. But this phenomenon is the common result of three different mechanisms, arising from three different histological and immunological conditions existing in these three infections.

In the case of *P. rouxi* there is an evident inability of the host to elaborate a level of immunity in the blood, sufficient to produce the parasitolytic crisis. The infection is continuously patent with a low parasitaemia showing little or no modifications from the first beginning through the entire course. Although an influence of the spleen on the rate of parasite multiplication in the blood cannot be denied, this action is much less marked than in other infections.

In the case of *P. elongatum* the situation is complicated by the simultaneous presence of a continuous source of parasites living in immunologically inert tissue cells (basophilic erythroblasts, haemocytoblasts, etc.) not reached by antibodies eventually present in the blood. In these conditions, in spite of the fact that many phagocytosing macrophages are often observable in haemopoietic tissues, the immunity response of the host is unable to modify the course of the infection.

In *P. gallinaceum* infections the R. E. S. of the host shows in a short time a complete resistance to parasite invasion. The mechanism by which this immunization is reached is likely to be the following. During the exoerythrocytic attack a great number of R. E. cells are destroyed. The cells that escaped invasion are the only ones that can multiply and replace the destroyed cells. It seems probable that the newly formed R. E. cells grow progressively more resistant to parasite invasion, resulting finally in totally immune cels. Simultaneously with the development of the complete immunity of the R. E. cells, the host is able to elaborate an immunity in the blood, sufficient to produce the immunity crisis of the erythrocytic forms: but latter the host is unable to maintain a state of immunity to such a grade, to kill all the parasites living in red cells. Therefore the erythrocytic forms continue to develop in small number during the whole life of the host. In chronic infections the blood parasites may fall to such a low level that routine blood examinations will fail to detect them, but their existence can always be checked by splenectomy or by inoculation to susceptible animals.

By this analysis, it can also be stated that these three bird parasites show no relapse in the spontaneous course. An increase in number of the parasites can only be obtained by splenectomy in *P. gallinaceum,* and, to a minor extent, in *P. rouxi.*

An immunity strong enough to liberate the host body from all the parasites is on the contrary successfully produced by the albino rat against *P. berghei.* Shortly, after the end of the primary attack of a blood-induced infection by *P. berghei,* all the plasmodia, until the last individual, are destroyed. Also in this case spontaneous relapse never occur

A different behaviour is shown by *P. cynomolgi* (and also by *P. vivax, P. ovale,* and, to a minor extent, *P. falciparum*). The immunity produced during the course of the infection from these Plasmodia is often unable to kill all the parasites living in red cells within a short time after the parasitolytic crises: some of the parasites survive, and soon as the immunity level in the blood collapses (for lacking of antigen production), they will multiply producing a relapse. Then the immunity level rises again (owing to the new antigen produced by the relapse), and the parasites become reduced in number. The fluctuation in number of the red cell parasites may continue for some time (usually short for *P. falciparum,* much longer for *P. cynomolgi* and *P. vivax),* until the common result is the complete disappearence of the parasites from the body of the host.

This mechanism is the only involved in blood-induced infections. In sporozoite infections the persistence of the cycle in the parenchyma cells of the liver is well established in *P. cynomolgi* by various experiments of Shortt, Garnham, Bray and their collaborators. More recently, Garnham and Bray have shown that the hepatic cycle of *P. cynomolgi* in immune monkeys is more vigorous and lasts longer than in susceptible monkeys, «possibly because under adverse conditions the parasite turns to the tissue stage of existence, where it lies protected from most hostile factors».

The forms inside the epithelial cells of the liver certainly contribute as a source of parasites for the invasion of red cells, when the immunity level in the blood decreases, and a higher rate of parasite multiplication in the blood may again take place. It is also possible that in some individuals these forms are the only surviving ones to continue the infection. But this is like to be an exceptional occurrence.

Many facts are in support of the opinion that red cell parasites alone can be sufficient to produce relapses. The following are here quoted:

1. The existence of long term relapses in blood-induced infections from *P. cynomolgi*. It is well known that in blood-induced infections schizogony in liver cells does not occur.

2. The existence of relapses in *P. falciparum* infections, where only one generation of pre-erythrocytic forms occurs in the liver, and late exoerythrocytic forms are completely absent.

3. The fact that during latency the blood is often infective to susceptible animals.

4. The fact that during latency the R. E. S. is continuously phagocytosing fresh (black) pigment.

The following general conclusions can finally be considered:

a) Spontaneous true relapses, so far as it is known, do occur in human and monkey parasites only.

b) The main condition for their occurrence is a lowered degree of immunity in the blood of the host. The source of parasites for the red cell invasion during the relapse is constituted by erythrocytic forms escaping the action of the antibodies, as well as by merozoites deriving from eventually persisting forms in the epithelial cells of the liver.

c) The different tissue cells involved as site of schizogony in Plasmodia infections can be immunologically classified as follows:

1. The R. E. cells, able to set up such a strong endocellular resistance, to become in a short time entirely immune to parasite invasion (*P. gallinaceum* and similar infections).

2. All the other cells (red cells, cells of the erythroblastic series, epithelial cells of the liver), which seem to be immunologically inert, no endocellular defense having yet been discovered in them. It seems likely that parasites living in these cells can only be affected by the antibodies existing in the plasma and brought around with the blood circulation. It happens therefore that parasites living in red cells are continuously under the action of the antibodies. On the contrary, those living in haemopoietic cells (*P. elongatum*) are almost completely protected against their action. Late exoerythrocytic parasites living in hepatic epithelial cells (in human and monkey plasmodia), are protected, while endocellular, from the action of the blood antibodies, but their merozoites, when liberated into the blood stream, must come in contact with the antibodies, at least for the short time elapsing until they can penetrate a more or less contiguous liver cell. The long term final result, in *P. cynomolgi* and *P. vivax,* is the complete destruction of all the parasites (in both the blood and the liver). It is, therefore, to be concluded that, if some sort of progressively growing endocellular immunity does not occur in hepatic parenchyma cells, the immunity existing in the blood should be regarded as the only form responsible of killing, finally, all the merozoites coming from both epithelial and red cells.

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BLOOD LOSS AND REPLACEMENT IN THE RODENT MALARIAS *PLASMODIUM BERGHEI* AND *PLASMODIUM VINCKEI*

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Acquired immune processes have been very intensively studied since the fundamental mechanism of antigen-antibody reactions was first worked out less than a century ago. Much is known about the types of cell taking part in them, the ways in which their products react with invading organisms, the site of these reactions and the dynamic interplay between the continuing development of the invader vis-a-vis the host mechanisms which oppose it.

Less work has been done on the intrinsically no less fascinating problems of variation in innate susceptibility. The bald statement is frequently made, with no further elaboration, that a given host is refractory to a certain parasite, while another phylogenetically similar host is highly susceptible. Defining the reasons for such differences should obviously lead to increased understanding of the disease process. Since it is possible to conceive of a great number of physiological factors which could underlie such differences, the responsible mechanisms must be separately defined for each host-parasite combination.

The present study is an attempt to define one such factor associated with innate immunity in plasmodial infections in rodents, namely, the age of the red cells available for invasion when the host is first exposed to the parasite; and to correlate this factor with processes of blood loss and replacement in response to infection, and with the acquisition of specific immunity, each of which is in a dynamic state of change from the moment when the parasite first enters the host body.

Certain plasmodia preferentially invade red cells of a given maturity (favoring either immature or definitive erythrocytes), whereas others are indifferent to the age of the red cell invaded. It was thought that

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the state of the red cell population, whether it was reticulocytic or normocytic at inoculation and during infection, might affect the innate susceptibility of a host which favored red cells of a given maturity, but ought to affect susceptibility less if the plasmodium in question was indifferent to red cell age.

A) *Grouping reticulocytes according to their age.*

When an attempt is made to define the age of the red cell invaded by a plasmodial merozoite it is soon seen that the term «reticulocyte», designating as it does all immature red cells in which reticulum can be demonstrated with the aid of brilliant cresyl blue, is too broadly inclusive to be of real use. One cannot equate the reticulocyte containing a granule or two of reticulum with the one packed to capacity with reticular substance. The former is in fact almost a definitive erythrocyte, while the latter is a very young red cell precursor. Subdivisions between these two extreme situations were therefore arbitrarily made, and five categories of mammalian reticulocyte were defined, from + to + + + + + in the order of increasing immaturity and reticulation. Each category contained roughly twice the quantity of reticulum in the category preceding (cf. Fig. 1).

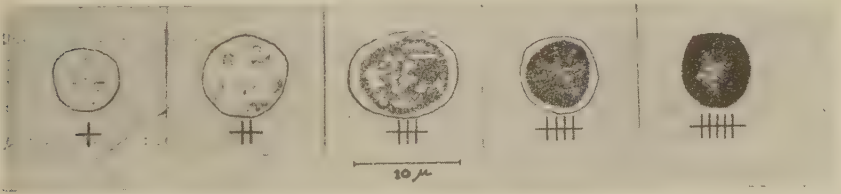

Fig. 1 — Camera lucida drawings of rat reticulocytes stained with brilliant cresyl blue and Giemsa's stain

An index was calculated in the following way to define the average age of a population of blood cells:

a) Four thousand red cells were classified in six categories ranging from definitive erythrocyte to + + + + + reticulocyte. Although a few normoblasts occurred for a day or two at the height of blood replacement, grading them on a similar scale would have greatly complicated calculations, as the reticulation of their cytoplasm varied widely. Since the normoblast numbers were negligible, only non-nucleated reticulocytes were included in the index.

b) The number of cells in each reticulocyte category was multiplied by a factor (= 1 for + reticulocytes, and rising by geometrical progression to = 16 for + + + + + reticulocytes).

c) The sum of the above products is defined as the *basophilic index,* and represents the total estimated amount of reticular substance in all classes of reticulocyte in a given population of 4,000 red cells.

TABLE 1 — *Computation of the basophilic indices of two populations of circulating erythrocytes which contain identical numbers of reticulocytes*

Blood film	Category	Observed number of reticulocytes per 4,000 erythrocytes	Factor representing relative amounts of reticulum	Basophilic index
A	+++++	80	16	1 280
	++++	140	8	1 120
	+++	240	4	960
	++	640	2	1 280
	+	0	1	0
	Total	1 100		4 640
B	+++++	20	16	320
	++++	20	8	160
	+++	120	4	480
	++	580	2	1 160
	+	360	1	360
	Total	1 100		2 480

Note that whereas the reticulocyte counts are identical, the basophilic indices are widely divergent.

Blood films containing identical numbers of reticulocytes may have widely varying basophilic indices (cf. Table 1).

When changes in basophilic index and percentage of reticulocytes during infections with rodent plasmodia are plotted against time, the two curves follow each other very closely during periods of mild reticulocytosis, but diverge widely when reticulocytosis is marked. No matter how

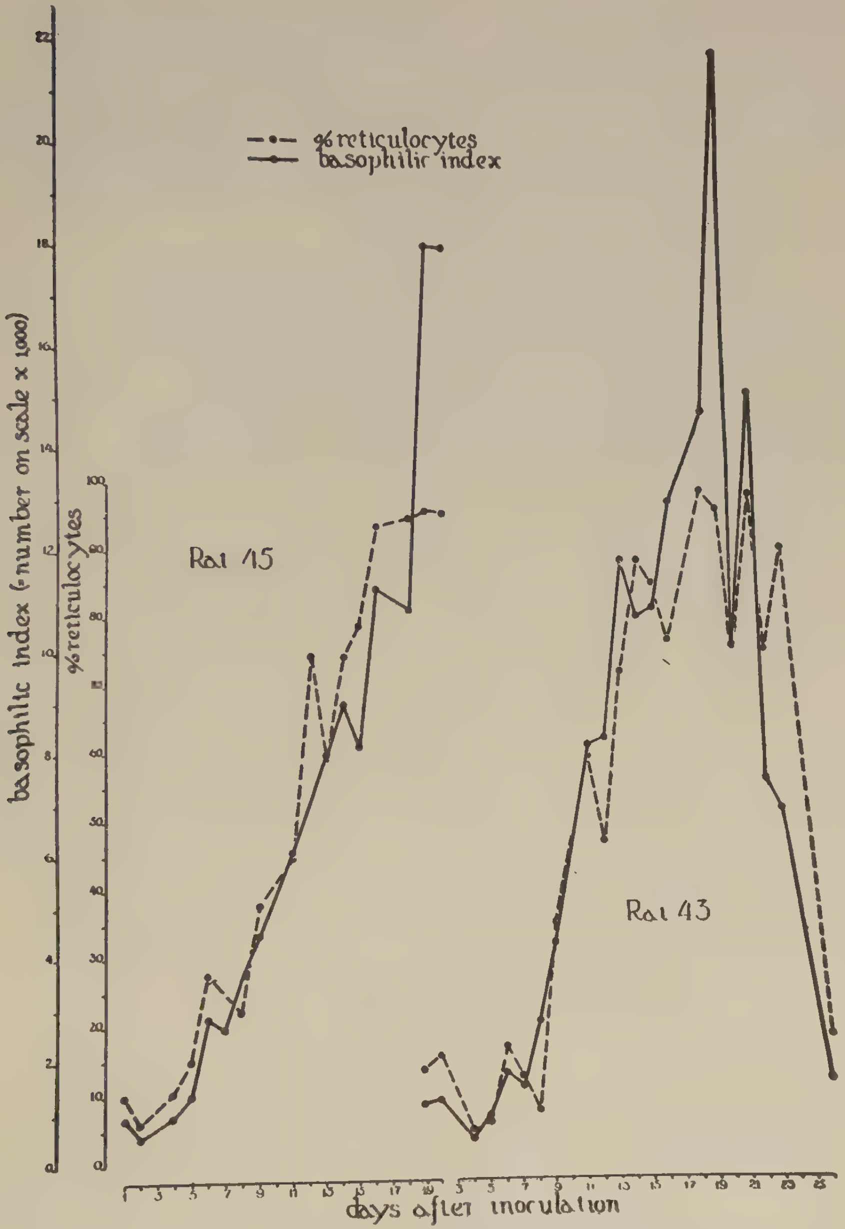

Fig. 2 — Divergence of percent reticulocytosis and basophilic indices at the height of reticulocytic repair in 3-week rats

intense the reparative response, the percentage reticulocyte curve cannot exceed the 100 % limit, which it may, however, approach as asymptote. The basophilic index curve, on the other hand, can and does rise to sharp peaks during such a period, as it is at such times that the very immature cells occur in the circulation, and the increasing weight given to more immature cells by progressively higher category factors stresses the intensity of the reaction (cf. Fig. 2).

In studying *P. berghei* and *P vinckei* in rats, daily observations were made of four variables before and during infections, and were continued through death or latency. The processes observed were:

1) Parasitemia — studied in Giemsa-stained films.

2) Erythrocyte counts — done in Thoma counting chambers.

3) Percentage of reticulocyte counts in films stained first with brilliant cresyl blue and counterstained with Giemsa's stain.

4) Basophilic indices computed as discussed above from the same films used for percentage reticulocyte counts.

Innate susceptibility was reflected in the slope of the parasitemia curve during the acute rise of infection. Parasitemia curves also yielded information on the timing of crisis, and therefore on the advent of effective acquired immunity.

The interplay of these variables was analysed in the following situations. Weanling and adult rats were infected with either of the two plasmodia, *P. berghei* or *P. vinckei*. Rats of different age infected with the same plasmodium were compared; as were rats of similar age infected with different plasmodia. In addition, *P. berghei* infections in mature rats with marked circulating reticulocytosis induced by cardiac bleedings were compared with infections in untreated controls of the same age.

B) P. berghei *in rats of varying age*[1].

It has generally been recognised that *P. berghei* favors reticulocytes over definitive red cells. When red cells which contain young merozoites in rats of all ages are classified as to their reticulation on the scale defined above, it is seen that *P. berghei* merozoites distinguish between reticulocytes of varying age, and favor the +++ reticulocyte and less mar-

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[1] A. ZUCKERMAN, *Jour. Inf. Dis.*, 100: 172-206, 1957.

TABLE 2 — *Types of blood cell present throughout patency of* P. berghei *and preferences of merozoites for invading cells of varying type*

Rats	Category of erythrocytes	RBC in given category/4000 RBC	Percent merozoites invading cells of given category
Adult, surviving	Normoblast	4.2 ± 2.30 (0.005)*	0.0 ± 0.00
(7 rats, 36 films)	Reticulocyte +++++	5.6 ± 2.62 (0.14)	0.0 ± 0.00
	++++	11.1 ± 3.46 (0.28)	1.5 ± 0.51
	+++	52.8 ± 7.59 (1.32)	53.9 ± 2.72
	++	177.8 ± 14.59 (4.45)	24.2 ± 2.61
	+	38.9 ± 6.84 (0.97)	3.6 ± 0.70
	Definitive RBC	3740.0 ± 37.43 (93.50)	14.7 ± 2.24
Young, surviving	Normoblast	44.4 ± 2.91 (0.76)	2.0 ± 0.03
(6 rats, 89 films)	Reticulocyte +++++	98.8 ± 17.22 (2.47)	1.2 ± 0.23
	++++	79.2 ± 9.56 (1.98)	12.0 ± 1.24
	+++	250.0 ± 26.02 (6.25)	63.8 ± 1.67
	++	1358.0 ± 104.81 (33.95)	8.9 ± 1.25
	+	53.9 ± 10.75 (1.35)	3.4 ± 0.52
	Definitive RBC	2118.0 ± 143.30 (52.80)	7.8 ± 1.33
Young, succumbing	Normoblast	40.9 ± 2.91 (0.51)	3.4 ± 0.53
(3 rats, 44 films)	Reticulocyte +++++	88.7 ± 15.74 (2.22)	3.0 ± 0.69
	++++	110.2 ± 15.38 (2.76)	20.1 ± 1.96
	+++	333.0 ± 45.49 (8.33)	58.2 ± 2.31
	++	1423.0 ± 132.44 (35.60)	4.9 ± 1.51
	+	20.4 ± 6.88 (0.51)	2.6 ± 0.67
	Definitive RBC	2001.0 ± 195.15 (50.00)	7.8 ± 1.68
Young, uninfected control	Normoblast	0.0 ± 0.00 (0)	
(1 rat, 24 films)	Reticulocyte +++++	0.0 ± 0.00 (0)	
	++++	2.1 ± 2.04 (0.05)	
	+++	31.2 ± 4.94 (0.78)	
	++	346.0 ± 30.32 (8.65)	
	+	95.8 ± 13.15 (2.39)	
	Definitive RBC	3501.0 ± 38.18 (87.70)	

Figures represent mean values obtained from blood films taken daily during patency from 7 adult and 9 young rats and from 1 young, uninfected control during a similar period.

* Numbers in parentheses represent percent of RBC.

kedly the + + and + + + + cell, while avoiding definitive red cells and reticulocytes of categories + or + + + + +. They are thus capable of distinguishing not only between cells with or without any reticulum; but between prospective host cells with slightly different degrees of reticulation, rejecting both those with extremely dense or extremely sparse reticulum. Whatever the mechanism of choice may be, whether physical or chemical, it must therefore be singularly sensitive.

The blood of normal weanling rats (age ca. 25 days) contains numerous circulating reticulocytes (about 20 %); whereas very few (about 4 %) are found in the blood of mature rats. Since ***P. berghei*** favors reticulocytes, the parasite is free to invade cells of its preference in the weanling, and the infection rapidly develops during the period of innate immunity, when merozoites, free in the plasma, meet with no specific host resistance to the invasion of clean reticulocytes. In response to the destruction of infected cells, a wave of repair reticulocytes enters the peripheral blood, beginning about a week after inoculation and rising to a peak after an additional week. This increasing reticulocytosis again favors parasitic reproduction, which continues unabated until crisis. After this point, specific acquired immunity controls parasitemia even in the presence of a highly reticulocytic blood population.

In the mature rat, whose normal blood contains few reticulocytes, *P. berghei* merozoites initially find themselves in a less favorable milieu than in the juvenile rat. They do, however, establish themselves in small numbers. A reticulocyte wave in response to the anemia of infection occurs at about the same time in the adult as in the weanling rat. But since parasitic crisis occurs earlier in the mature than in the juvenile rat, effective acquired immunity checks parasitemia even though the circulation is suddenly flooded with reticulocytes. Crisis forms, appearing at this time, bear witness to the fact that even merozoites which have succeeded in penetrating clean cells were injured in transit through the plasma, and cannot therefore continue their normal development.

Reticulocytic replacement was thus seen to occur according to a relatively stable rhythm regardless of the age of the rat, commencing during the second week after inoculation, and reaching a peak during the third. Immune crisis, on the other hand, occurred early (during the first week) in mature rats; and late (after the second week) in weanlings. A reticulocyte wave which appears before crisis, as in the juvenile rat, therefore endangers the host, which is not yet equipped with effective acquired immunity; but such a wave which appears after crisis, as in the mature rat, is a matter of relative indifference to the host, whose acquired immunity is sufficient to deal with the parasites even in the presence of a shower of their favored cells.

In addition to the very marked reticulocytic responses accompanying heavy infections of *P. berghei,* clearly defined responses were associated with even very low-grade parasitemias in mature rats. The reason for this is that blood destruction, particularly in mature rats, was far in excess of that directly attributable to parasitemia. The divergence between observed red cell counts corrected to disregard replacement

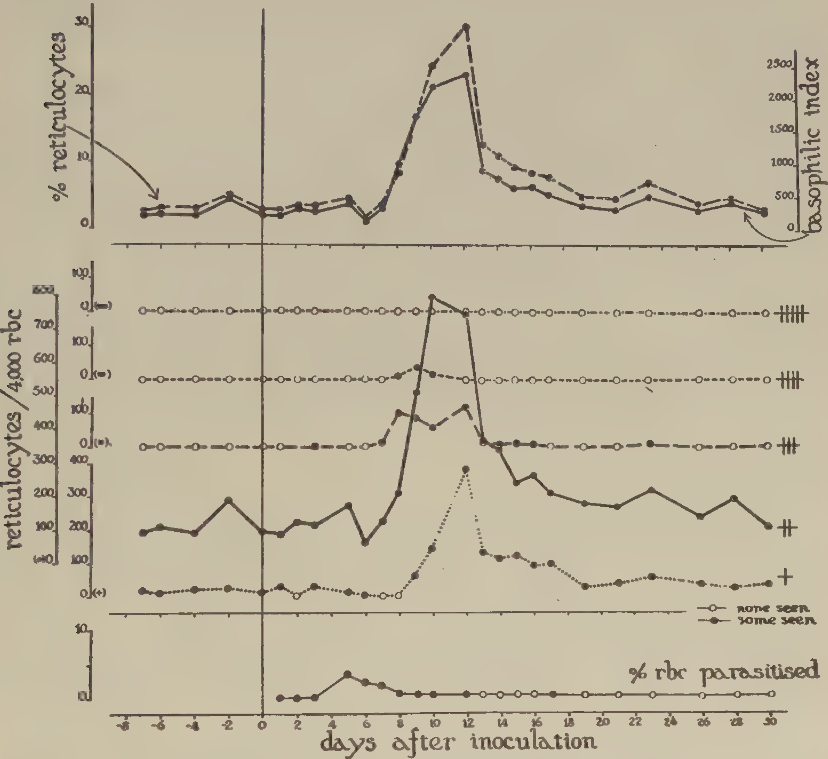

Fig. 3 — *P. berghei* in a mature rat: correlations between the nurse of parasitemia and reticulocytic response to infection

reticulocytes and estimates of changes in the original blood cell population due to direct destruction of erythrocytes by emerging parasites is very wide in mature rats. Some agency other than direct rupture by developing parasites destroys a significant portion, about a third, of the mature rat's blood. Since practically the entire original circulating erythron in young rats with high parasitemias was directly destroyed by parasitic rupture, excessive rupture by this additional agency was difficult to assess in young rats. But in mature rats, with insignificant parasitemias, the extremely high excessive blood loss was very striking (see Fig 4).

It is thought likely that a lytic auto-antibody, produced by the rat in response to its own altered red cells, may be the agent responsible for the excessive loss. Experiments to prove or to disprove this hypothesis are now being done. Should this prove to be the mechanism, the rodent malarias would join the growing series of diseases whose pathology is thought to be associated with auto-antibody.

When mature rats are rendered anemic and reticulocytic by repeated cardiac bleeding before inoculation, their infection courses resemble those of weanling rats and not of mature untreated rats in the following ways:

1) Their innate immunity is low due to the presence of significant numbers of reticulocytes before immune crisis, and initial parasitemias are therefore severe.

2) In some (3 out of 10) the acquisition of immunity was disturbed, and these died of fulminating infection with no crisis, as did 3 out of 9 weanlings. This is in marked contrast to the regularly benign nature of the infection in untreated mature rats.

3) Due to their high parasitemias, all the observed blood loss in bled mature rats, as in weanlings, was attributable to direct parasitic rupture.

C) P. berghei *compared with* P. vinckei *infections in rats of varying age*[1].

P. vinckei infections in mature and weanling rats were relatively less severe than *P. berghei* infections, with lower parasitemias, shorter duration, and less extensive anemia followed by less extensive reticulocytosis. Indeed, no observable reticulocytic responses followed either the extremely low-grade parasitemias in mature rats (less than 1 % peak), or the less severe of the weanling rat infections (i. e., those up to 5 % peak).

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[1] A. ZUCKERMAN, *Jour. Inf. Dis.*, 103: 205-224, 1958.

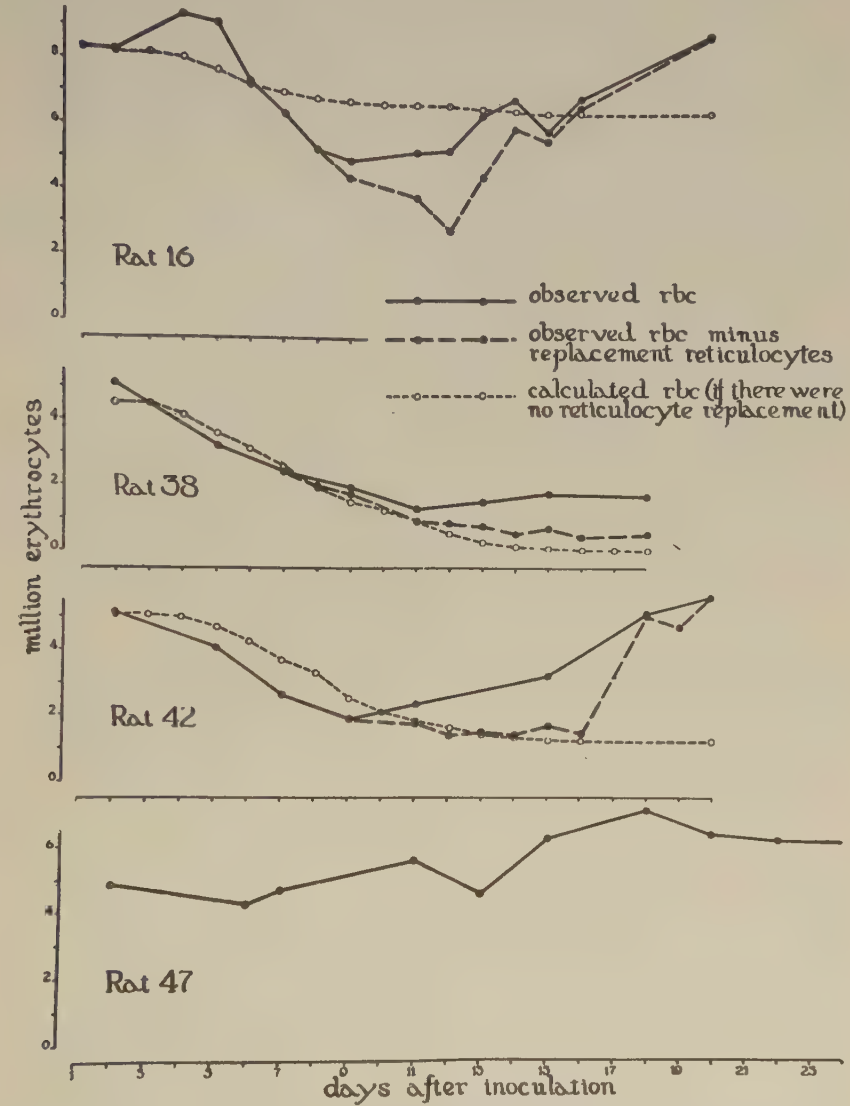

Fig. 4 — Red cell counts in an untreated, young rat (rat 47), in a mature rat (rat 16) during and following infection with *P. berghei;* in a succumbing young rat (rat 38) and in a surviving young rat (rat 42)

P. vinckei differs from *P. berghei* in its host cell preference. We have seen that *P. berghei* favors reticulocytes of a given age, regardless of their availability or scarcity during variations in the state of the blood cell population accompanying infection. *P. vinckei,* on the other hand, tends to adapt to the vicissitudes of the blood cell population, and invades as if by chance cells of the currently dominant type. It is therefore indifferent to the age of the host cell it invades. Since the definitive red cell is generally the dominant types *P. vinckei* merozoites most frequently invade this cell. But when reticulocytes are in the ascendant, its preference shifts to them. Thus, whereas *P. berghei's* preference is stable and constant, *P. vinckei* tends to shift its preference in response to the changing state of the blood cell population.

In *P. berghei* we have seen that host cell preferences play a definite role in determining innate immunity. The weanling rat, with many reticulocytes, is a better culture medium for *P. berghei* than the mature rat, with few. In contrast, since *P. vinckei* merozoites invade whatever red cells happen to be available, host cell preferences cannot explain either the marked innate immunity of rats of all ages to this parasite, or the fact that younger rats are, nevertheless, more susceptible than mature rats. Thus, although host cell preference is a factor in innate immunity to *P. berghei,* factors other than this one must govern innate immunity to *P. vinckei.*

That innate immunity is capable of being disturbed in *P. vinckei*-infected weanlings is shown by the fact that in 3 weanlings succumbing to infection parasitemia curves were steep and fulminating, and deaths occurred within the first week; whereas in 14 surviving infections curves rose in a gentle slope during the same period.

Processes of blood loss were strikingly similar in the two rodent malaria. In *P. vinckei,* as in *P. berghei,* loss of blood in excess of what can be attributed to direct rupture by parasites was observed, and was particularly marked in mature rats. Thus, while emerging parasites destroyed less than a hundreth of a percent of the circulating erythron, more than 15 % of the blood was actually lost in mature rats. Excessive loss was also observed, but to a lesser degree, in weanling rats with *P. vinckei.* Where parasitemias are severe, destruction due to an agency other than parasitic rupture could possibly be masked by the extensive direct rupture. Thus whether excessive loss appears to be less marked in juvenile rats due to masking by direct rupture; or, whether the postulated auto-immune agent is actually of lower titre in young than in mature rats, cannot at present be clearly stated. The same auto-antibody mechanism of excessive red cell destruction is postulated for both of the rodent plasmodia.

The rodent malaria study constitutes part of a larger series designed to explore similarities and differences among processes of blood loss and replacement in response to mammalian and avian plasmodia. In several simian malarias for which data have already been analysed (namely, *P. cynomolgi, P. gonderi* and *P. knowlesi* in the rhesus monkey), the observed results closely parallel those obtained with the rodent malarias[1]. In particular, blood loss in excess of that due to direct parasitic rupture is a conspicuous feature in all three.

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[1] A. ZUCKERMAN, *Jour. Inf. Dis.*, 106: 123-140, 1960.

VIRULENCE DES PLASMODIUMS ET RÉSISTANCE DE LEURS HÔTES NATURELS, INSECTES ET VERTÉBRÉS

EDMOND SERGENT

Mon dessein est d'exposer quelques-uns des faits qui nous ont particulièrement intéressés, Etienne Sergent et moi, au cours de 58 années d'étude expérimentale de l'épidémiologie et de la prophylaxie du paludisme des Oiseaux à *Plasmodium relictum* et du paludisme des Rongeurs à *P. berghei*. Ce sont des considérations personnelles sans développement historique des questions.

Notre étude de l'épidémiologie du paludisme a débuté, en 1900, par la répétition des expériences qui avaient conduit Ronald Ross en 1897-1898 à sa découverte du rôle des Moustiques dans la transmission du paludisme des Passereaux. En même temps, nous vérifions la constance de ce que nous avons appelé la «loi de Grassi»; «pas de paludisme sans anophélisme», en constatant la présence d'Anophèles dans des régions palustres d'Algérie que des publications prétendaient indemnes de ces Moustiques. À la même époque, en 1900-1901, nous montrions l'existence en France d'un «anophélisme sans paludisme» dans la Vallée de la Seine, et à Paris même.

I. — PRIMO-INFECTION ET RÉSISTANCE INNÉE

LA PLASMODIE CHEZ SON HÔTE INTERMÉDIAIRE, LE MOUSTIQUE

1. — *Spécificité parasitaire et Résistance innée.* — Une des caractéristiques du parasitisme, défini comme une association étroite entre deux êtres animés différents, — dont l'un, le parasite, vit aux dépens de l'autre, qui est appelé son hôte, — est la spécificité de cette association; elle a lieu toujours entre espèces déterminées.

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 46-58, 1959

(P. relictum). — Nous avons pu obtenir au laboratoire l'évolution sporogonique complète de *P. relictum* chez les Culicines des environs d'Alger que nous avons soumis à cette expérience: *Culex pipiens*, — *Aedes aegypti* (= *Stegomyia fasciata*), — *Culex impudicus* (= *Culex sergenti* Theobald, 1903), — *Allotheobaldia longiarolata* (Macquart, 1838) (= *Theobaldia spathipalpis*), — *Aedes (Ochlerotatus) mariae* Sergent, 1903, dont les larves vivent dans l'eau de mer.

2. — Il n'y a *pas de parallélisme* entre l'infection sanguine de l'Oiseau et l'infection consécutive du Moustique qui le pique. L'infection paludéenne d'un Oiseau contaminé par piqûre de Moustique n'est pas non plus en rapport avec le nombre de sporozoïtes qu'il reçoit.

3. — *Un lot de Moustiques* qui a piqué une seule fois un Canari infecté par *P. relictum peut* ensuite *contaminer successivement deux et même trois sujets* neufs après un intervalle de quelques semaines.

4. — *(Plasmodies humaines)*. — *L'indice sporozoïtique* relevé chez des *A. maculipennis labranchiae* dans des régions très paludéennes d'Algérie a varié de 4 à 10 %. L'expérience nous a fait considérer que dans ce pays un indice sporozoïtique de 4 % correspondait au *seuil de danger* (de même qu'un indice splénique de 10 %).

5. — *Influence de la température. (Plasmodies humaines)*. — Certaines années, en Algérie, l'opinion publique a été vivement émue par l'apparition d'épidémies sur les hautes montagnes, d'ordinaire indemnes. On a pu se rendre compte de la coincidence de ce «paludisme des hauteurs» avec des périodes, dépassant une semaine, où a soufflé sans interruption le sirocco, vent brûlant du Désert, car la sporogonie des Plasmodies n'évolue chez les Anophèles qu'à une température supérieure à 17°. Or, en temps normal, les lieux élevés bénéficient d'un refroidissement nocturne. *(P. relictum)*. — Les expériences avec *P. relictum* nous ont montré qu'une température de 12° maintenue plus de 3 jours n'est pas suffisante pour permettre l'évolution sporogonique de la Plasmodie chez le Moustique.

6. — Nous avons observé assez souvent que *la piqûre* d'Anophèles: *A. maculipennis, A. hispaniola*, pouvait n'être pas perçue. Il n'en est pas de même des piqûres de Culicines.

7. — *(Plasmodies humaines)*. — Le *vol saccadé* d'un *A. maculipennis* ou d'un *A. algeriensis* diffère du *vol ondulant* d'un Culex ou d'un Aëdes.

LA PLASMODIE CHEZ SON HÔTE DÉFINITIF, LE VERTÉBRÉ

1. — *Spécificité parasitaire. Résistance innée.* — Comme les diverses espèces de Moustiques, les diverses espèces de Vertébrés sont inégalement sensibles à l'infection par les Plasmodies. Cette «spécificité parasitaire» traduit soit une *résistance innée absolue* (le parasitisme est impossible) (Ex.: contre *P. berghei,* Cobaye adulte, Gerbille, Hérisson, Canari), — soit une *résistance innée relative* (le parasitisme est possible, mais pas toujours mortel) (contre *P. berghei,* Rat blanc, Mérion) (contre *P. relictum,* Canari), — soit une *résistance innée impuissante* (parasitisme mortel) (contre *P. berghei,* Souris blanche).

2. *Résistance innée des hématies à la pénétration des mérozoïtes.* — H. Galliard a montré, le premier, en 1949, que les mérozoïtes de *P. berghei* inoculés à un Rongeur neuf attaquent bien plus souvent les hématies immatures polychromatophiles que les normocytes. D'après nos observations, cette préférence vient de ce que les polychromatophiles, qui apparaissent souvent comme déformés, avec des contours sinueux, doivent avoir une consistance molle et une cuticule mince que les mérozoïtes peuvent percer plus facilement que celle des normocytes, dont la forme circulaire montre la solidité.

Cette propension à l'attaque des polychromatophiles dont font preuve les Plasmodies contraste avec un fait curieux. Le cytoplasme basophile des hématies polychromatophiles n'est pas un milieu de culture propice à la vie et à la multiplication des Plasmodies. Celles-ci s'y étiolent, tandis qu'elles évoluent normalement dans le cytoplasme acidophile des normocytes (comme aussi des réticulocytes).

3. L'évolution de la Plasmodie chez le Vertébré comporte toujours 3 stades: incubation, accès aigu, stade métacritique latent.

A) *L'incubation est caractérisée par l'absence de symptômes morbides, — l'absence de Plasmodies visibles dans le sang de la circulation périphérique, — et par l'absence d'une action thérapeutique de la quinine.*

Le point de départ de nos recherches sur l'action de la quinine a été le désir d'établir par la méthode expérimentale la meilleure technique de quininisation préventive contre le paludisme humain.

Nous avons pensé, en 1920, à appliquer l'étude expérimentale de la quininisation à un autre paludisme que celui de l'Homme. Le paludisme des Passereaux dû à *P. relictum,* qui a servi à Ronald Ross pour la découverte du rôle des Moustiques dans la propagation du paludisme, remplissait les meilleures conditions pour cette étude.

Dans nos expériences, nous n'avons obtenu aucun résultat quand le traitement quinique du paludisme des Oiseaux était appliqué au cours de l'incubation de l'infection.

Notre découverte de *l'inefficacité du traitement antipaludique pendant l'incubation* fut confirmée ensuite par différents chercheurs expérimentant sur des Plasmodies humaines ou sur d'autres Plasmodies aviaires, comme le rapportent L. Verney[1] et P. C. C. Garnham[2].

Evolution des sporozoïtes pendant l'incubation. — Une foule de paludologues (dont nous étions) a cherché en vain depuis 1900 à voir au microscope la pénétration des sporozoïtes dans les hématies.

Un mystère enveloppait le sort des sporozoïtes entre le moment où ils étaient inoculés par l'Insecte au Vertébré et le moment où les premiers parasites apparaissaient dans les globules rouges. Que deviennent les sporozoïtes, minces fils de 12 à 15 μ de longueur, pendant cette «incubation parasitaire» d'une durée de quelques jours? Comment se transforment-ils en ces petits anneaux intraglobulaires de 2 μ environ de diamètre que sont les jeunes trophozoïtes?

L'explication de cette particularité, ainsi que du phénomène de l'inefficacité complète de la quinine dans le paludisme pendant la période d'incubation fut mise en lumière lorsque furent découvertes, par plusieurs expérimentateurs, les «formes exérythrocytaires», dont Raffaele est le premier à avoir reconnu la signification.

Nous avons recherché les formes exérythrocytaires dans les organes internes de centaines de Canaris anciens paludéens, qui avaient succombé à une mort naturelle. Douze (5 %), montrèrent des formes exérythrocytaires. Nos observations établissaient définitivement deux points qui avaient été discutés: *a*) les formes exérythrocytaires ont apparu dans une souche de Plasmodie transmise depuis 16 années par inoculation de sang, sans passage par le Moustique; *b*) ces formes ont apparu chez des Canaris en état d'infection latente métacritique depuis plus de 2 ans après l'inoculation infectante (laps de temps considérable, si l'on songe que la durée moyenne de la vie d'un Canari est de 7 a 9 ans).

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[1] Lorenzo VERNEY — Lo sviluppo dei parassiti malarici nel reticuloendotelio, *Ann. Ig.*, **48**, 26-40, 1938.

[2] P. C. C. GARNHAM — Exoerythrocytic schizogony in malaria, *Trop. Dis. Bull.*, **45**, 10, 831-844, 1948.

B) *Pendant l'accès aigu ou crise,* à la différence de ce qui se passe pendant l'incubation, *les médicaments antipaludiques exercent une action thérapeutique.* Lorsqu'en 1920 nous avons entrepris l'étude expérimentale de l'action des sels du quinquina sur le paludisme des Passereaux à *P. relictum,* nous avons été très surpris de constater que la quinine qui n'avait exercé aucune action thérapeutique pendant l'incubation de la maladie, possédait au contraire, quand on l'injectait pendant l'accès aigu, une efficacité curative analogue à celle qu'elle exerce dans les paludisme humains [1]. Cette action curative sur les *P. relictum* pullulant dans le sang de Canaris au cours de l'accès aigu est manifeste.

Nous avons ensuite établi, par tâtonnements, la dose de quinine tolérée par l'organisme, dont l'administration *préventive* est capable d'empêcher le développement de l'infection.

Ces recherches préliminaires ayant démontré l'exactitude, en même temps que la commodité, de la méthode d'essai des médicaments antipaludiques consistant à expérimenter sur des Canaris infectés au laboratoire avec *P. relictum,* nous l'avons appliquée à un certain nombre de produits pharmaceutiques, et d'autres chercheurs l'ont immédiatement adoptée.

Notre méthode d'essai des remèdes sur les Canaris paludéens a été employée dès le début par Schuleman, ainsi que par Fourneau, et conduisit les chimistes à la découverte d'excellents produits antipaludiques synthétiques.

Cas exceptionnels de résistance à la quinine, acquise par les Plasmodies. — Nous avons observé les premiers, comme l'ont rappelé Ann Bishop et Betty Birkett [2], le phénomène de la résistance qu'une souche de *P. relictum,* jusque là sensible à laction de la quinine, a *acquise,* à un moment donné, contre le traitement quinique. Il s'agit d'une Plasmodie que, dans une expérience effectuée en 1920, a résisté à une quininisation à petites doses poursuivie pendant 9 mois. Cette résistance à la quinine a été transmise pendant 2 passages successifs de cette souche à des Canaris inoculés avec du sang parasité, mais la souche est redevenue, au 3^e passage, sensible au médicament, quoique à un degré moindre que les autres souches.

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[1] P. KOPANARIS avait déjà signalé, en 1911, cette action de la quinine sur les parasites du sang périphérique dans le paludisme aviaire à *P. relictum.*

[2] A. BISHOP et B. BIRKETT — Acquired resistance to paludrine in *Plasmodium gallinaceum,* Acquired Resistance and Persistence after Passage though the Mosquito, *Nature,* 159, voir p. 884, 28 Juin 1947.

Morphologie des Plasmodies. — Plasmodies sans pigment: sur 13.934 *P. berghei* dont l'évolution schizogonique dans des hématies mûres offrait les caractères du cycle classique, 6.722, soit 48,2 %, étaient pigmentés et 7.212, soit 51,7 %, étaient dépourvus de pigment.

Des trophozoïtes binucléés et du pluriparasitisme sont assez souvent observés dans le paludisme à *P. berghei.*

Formes de dégénérescence. — *P. berghei* montre, dans les hématies immatures polychromatophiles, des formes schizogoniques singulières, déjà signalées par G. Fabiani, caractérisées par la configuration de la chromatine, qui n'apparaît que sous l'aspect de grains ponctiformes, dépourvus de cytoplasme individualisé dans la moitié des cas.

Anémie. — Au cours de l'accès aigu, le nombre des hématies tombe, en quelques jours, de 10 ou 12 millions à 1 ou 2 millions chez une Souris qui va mourir, et à 3 millions environ chez un Rat qui résiste et survivra.

Perte de la sexualité. — La souche de *P. berghei* que nous a donnée l'Institut de Médecine Tropicale d'Anvers, en janvier 1950, et que nous conservons depuis 8 ans par 750 passages de sang par Souris, ne nous montre plus de gamétocytes sur les préparations de sang colorées. La souche est devenue exclusivement sanguicole et sa prolifération est désormais asexuée.

Virulence. — Fixité de la virulence des Plasmodies: notre sauche de *P. berghei,* entretenue au laboratoire par des inoculations en série du sang de Souris blanches infectées à plus de 2.400 Souris blanches indemnes, a conservé, après 750 passages, au cours de 8 années, sa virulence (durée de l'accès 9 jours 2 — mortalité 100 %). Cette souche n'a jamais montré, en quelque saison que ce fût, d'exaltation ni d'atténuation.

Nous avons fait la même constation avec *P. relictum* conservé chez des Canaris. La virulence de *P. relictum* est fort variable suivant les souches, mais celle d'une même souche est fixe dans les différents passages successifs par Canari.

Idiosyncrasies. — Nous avons vu, en étudiant la «spécificité parasitaire» dans le paludisme à *P. berghei* des exemples étonnants de la variété des susceptibilités individuelles présentés par les Rats blancs, dont 7 %, aussi sensibles que des Souris blanches, meurent en quelques jours au cours d'un accès parasitaire suraigu, — et dont d'autres (7 % également) sont aussi réfractaires que des Cobayes et ne présentent aucun accès parasitaire visible. Entre ces deux cas extrêmes, beaucoup de variétés individuelles.

Occultation parasitaire. — La coexistence de *P. relictum* et de *P. rouxi* dans le sang des Moineaux algériens nous a fourni l'occasion de constater le phénomène de l'occultation parasitaire. *Plasmodium rouxi* que nous avons décrit en 1928 avec A. Catanei a des caractères spécifiques très nets, morphologiques et expérimentaux (par l'épreuve des réinoculations croisées). Dans notre laboratoire, *P. rouxi* et *P. relictum* mènent depuis trente-deux ans une vie en commun chez des Canaris inoculés en série. Cette association n'a modifié en rien les caractères spécifiques de chacun d'eux, mais elle donne des exemples du phénomène que L. Parrot a décrit sous le nom d'«occultation parasitaire» à propos de Plasmodies humaines et aussi de Piroplasmes bovins: nous avons souvent observé, chez des Oiseaux inoculés à la fois avec *P. rouxi* et *P. relictum,* qu'un accès parasitaire à *P. rouxi* seul se déroulait d'abord et que *P. rouxi* disparaissait dès que les *P. relictum* se montraient et provoquaient un accès parasitaire aigu.

Sortie de microbes latents. — Nous avons observé un phénomène en quelque sorte inverse dans une série d'expériences sur des Canaris qui n'avaient jamais montré de *P. rouxi* dans le sang de la circulation périphérique. Inoculés avec une souche de *P. relictum,* ils ont présenté un accès parasitaire aigu de cette Plasmodie. Une dizaine de ces Canaris, réinoculés plus tard avec *P. relictum* après un laps de temps variant de 1 à 5 ans, ont présenté un «accès de prémuni» à *P. relictum,* et en même temps, pour la première fois, des *P. rouxi.* Ceux-si devaient donc provenir de microbes latents, qui sont «sortis» à l'occasion d'une infection intercurrente.

Association de Plasmodies et de Spirochètes. — L'influence favorable exercée chez des malades de paralysie générale par l'impaludation thérapeutique a suscité les expériences suivantes.

A. Catanei a associé, chez des Canaris, *Spirochaeta gallinarum* (spirochétose des Poules) à *P. relictum.* La Plasmodie ne paraît pas avoir eu d'influence sur l'évolution de la spirochétose, mais les Spirochètes ont augmenté la gravité des infections à Plasmodies.

L'association expérimentale chez le Rat blanc de la spirochétose hispano-nord-africaine et du paludisme des Rongeurs à *P. berghei* n'a pas modifié, à un degré appréciable, l'évolution de l'une ou l'autre infection, — notamment un accès aigu de l'une n'a pas réveillé l'infection latente de l'autre. Elles ne se sont pas montrées antagonistes, et leur coexistence n'a pas modifié sensiblement leur virulence propre.

C) *Le cycle évolutif des Plasmodies, dans le paludisme des Oiseaux et dans celui des Rongeurs, comporte, comme celui des paludismes humains, un Troisième stade «métacritique» d'infection latente.*

Lorsque la résistance innée du Vertébré l'a fait triompher de l'attaque des Plasmodies et qu'il survit, sa victoire n'est pas complète.

Après la fin de l'accès aigu, l'hôte et le parasite se tolèrent mutuellement pendant parfois très longtemps. Trève armée, au cours de laquelle l'hôte a recouvré toutes les apparences de la santé et la Plasmodie, disparue du sang circulant, mène, dans les organes internes, une vie ralentie, coupée de retours offensifs (les rechutes) lorsque la résistance de l'organisme défaille.

Ce troisième stade métacritique latent a été observé, dans nos expériences:

a) chez tous les Canaris qui ont survécu à l'accès aigu de l'infection à *P. relictum,* soit chez 94 sur 100 inoculés (6 étant morts pendant l'accès aigu);

b) chez tous les Rats blancs adultes qui ont survécu à l'accès aigu de l'infection à *P. berghei,* soit chez 90 sur 100 inoculés (10 étant morts pendant l'accès aigu).

De l'infection latente d'emblée. — On s'aperçoit, de plus en plus, que dans un grand nombre de maladies contagieuses, le stade d'infection aiguë peut manquer après la contamination. Le parasite s'installe dans l'organisme de son hôte sans que celui-ci réagisse d'une façon visible. Ces cas où l'infection s'établit du premier coup sous une forme latente, asymptomatique, muette, s'observent dans les maladies dues à toutes les catégories de microbes: bactéries, rickettsies, champignons inférieurs, ultravirus (constatations de plus en plus fréquentes), protozoaires.

En ce qui concerne l'infection paludéenne, Laveran a écrit en 1907 pour le paludisme humain: «Les hématozoaires du paludisme peuvent rester *latents aussi bien chez des sujets qui n'ont jamais présenté de symptômes de paludisme* que chez ceux qui ont eu une ou plusieurs atteintes de fièvre» [1].

Nous employons, depuis 1910, pour désigner ces cas où l'accès aigu d'invasion manque, où l'infection reste silencieuse de bout en bout de son évolution, l'expression d'*«infection latente d'emblée»*.

Nous avons constaté de nombreux cas d'«infection latente d'emblée» dans le paludisme expérimental des Oiseaux à *P. relictum* et dans celui des Rongeurs à *P. berghei*.

De la durée des infections latentes. — Je citerai, comme exemple d'une longue infection de *P. berghei,* l'observation d'un Rat blanc qui, inoculé à l'âge de 5 mois, meurt de mort naturelle à l'âge de 24 mois et qui est trouvé porteur de Plasmodies. Son infection a donc duré 19 mois (plus des 3/4 de la vie moyenne d'un Rat), et jusqu'à la mort.

Dans nos expériences sur le paludisme à *P. relictum* des Canaris, dont la longévité moyenne est de 7 ans, les infections latentes les plus longues ont été constatées chez trois Canaris arrivés à un âge avancé et dont l'infection était entrée dans sa sixième année: 61 mois, 66 mois, 70 mois après la date de l'inoculation. Les infections latentes durant de 4 à 5 ans ne sont pas rares.

De la forte virulence potentielle possédée par des Plasmodies latentes dans les organes internes. — Pendant la longue période de trêve armée entre la Plasmodie et son hôte, qui s'écoule après la terminaison de l'accès aigu, le parasite végète, se reproduit petitement, mène une vie ralentie, mais sa virulence s'est seulement assoupie, elle ne s'est pas atténuée. Souvent, la virulence de Plasmodies latentes prélevées chez un sujet infecté depuis longtemps est bien plus violente que la virulence de Plasmodies prélevées au même sujet au cours de son accès aigu de première invasion.

Ce fait rappelle une remarque de Pasteur écrite en 1880: «N'oublions pas (...) ce fait vraiment remarquable que le maximum de virulence dans le microbe du choléra (des poules) nous a été offert par le microbe retiré des poules malades de cette affection lorsqu'elle est à l'état de maladie chronique. Il semble donc que, plus est prolongée dans le corps de l'animal la présence du petit parasite, plus grande devient sa virulence»[1].

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[1] *Traité du Paludisme,* 1907, 2^{e} édition, voir p. 222, Masson, édit., Paris.

Procédés de décèlement des infections latentes -- L'existence d'une infection latente dans le paludisme à *P. relictum* a été recherchée à l'aide de trois sortes de techniques. Les résultats de deux d'entre elles: 1) examen microscopique du sang circulant ou des organes, qui ne peut porter pratiquement que sur 15.000 hématies, soit un deux-cent-millième environ de la quantité totale du sang; — 2) inoculation à des Canaris neufs de un cinquième du volume total du sang, prélevé par une saignée partielle, — ne sont valables que s'ils sont positifs. La troisième technique seule donne des résultats certains, qu'ils soient positifs ou négatifs: inoculation à des Canaris neufs de la masse totale du sang, additionnée du produit de broyage d'organes internes.

La recherche des infections latentes de *P. berghei* chez des Rongeurs a comporté, dans nos expériences, les mêmes sortes d'investigations systématiques que celles des infections latentes de *P. relictum* chez des Oiseaux.

II. — RÉ-INFECTION ET RÉSISTANCE ACQUISE

LA PLASMODIE RÉINOCULÉE À SON HÔTE INTERMÉDIAIRE, LE MOUSTIQUE

Une infection plasmodique arrivée au terme de son cycle sporogonique (stade de sporozoïte) chez un Culicine n'empêche aucunement l'évolution normale chez ce même Moustique de gamètes ingérés plus tard au cours de nouveaux repas sanguins.

Des Culex qui ont piqué un premier Canari infecté par *P. relictum* et qui, des jours, des semaines, jusqu'à 4 mois plus tard, sucent le sang d'un autre Canari infecté, sont sacrifiés: on trouve chez eux des sporozoïtes dans les glandes salivaires et, en même temps, des zygotes de différents âges dans l'estomac. Une première infection ne confère donc aucune résistance à un Culex contre une nouvelle attaque des *P. relictum*.

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[1] *Oeuvres de Pasteur*, **7**, voir p. 54, Masson, édit., Paris.

LA PLASMODIE RÉINOCULÉE À SON HÔTE DÉFINITIF LE VERTÉBRÉ

Deux cas se présentent:

1. — La Plasmodie est réinoculée à un Vertébré qui a guéri cliniquement de son infection aiguë, mais qui en est au stade métacritique de son infection latente.

2. — La Plasmodie est réinoculée à un Vertébré dont la guérison a été non seulement clinique mais parasitaire. Son infection latente métacritique est terminée: il est déparasité.

1. — *Sujet réinoculé au cours du stade métacritique, c'est-à-dire lorsqu'il est en état d'infection latente.*

Si l'on réinocule à un Canari porteur de Plasmodies latentes la même espèce de Plasmodies, les parasites nouveaux venus n'ajoutent pas leur action à celle des microbes latents: «la place reste au premier occupant». C'est ce que nous avons appelé la «loi de préséance».

Dans toutes nos expériences, les Canaris qui avaient survécu à un accès de première invasion de paludisme à *P. relictum* ont opposé à toute réinoculation de la même Plasmodie une résistance nette. Mais cette résistance n'est pas complète, ce n'est pas une immunité absolue, elle est relative: la réinoculation ne cause pas en règle un accès clinique et parasitaire aigu violent comme chez les témoins, mais elle peut être suivie de l'apparition fugitive, dans le sang, de parasites extrêmement rares. C'est pourquoi nous avons employé, depuis 1910, pour désigner cette sorte de résistance acquise, l'expression d'*imunité relative* dont s'étaient servi, en 1901, Albert Plehn à propos du paludisme humain, et ensuite Th. von Wasielewski, à propos du paludisme des Passereaux à *P. relictum*[1]. Pour éviter toute confusion avec l'immunité vraie, nous avons proposé, plus tard, en 1924, avec L. Parrot et A. Donatien, de désigner cet état de résistance particulier par le terme de *prémunition*.

Les Rats blancs inoculés avec *P. berghei* présentent les mêmes phénomènes de prémunition que les Canaris inoculés avec *P. relictum*.

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[1] On trouve l'expression d'*immunité relative* sous la plume de PASTEUR, en avril 1881, à propos de l'immunité acquise contre le choléra des poules, qui est tout-à-fait «variable avec l'intensité de virulence du virus qui frappe». (PASTEUR, *Oeuvres*, **7**, pp. 56-59, Masson, édit., Paris).

Accès de prémunis. — Au cours de l'infection latente des prémunis il peut se produire non seulement des réveils des foyers microbiens qui couvent, mais aussi, lorsque les conjonctures extérieurs s'y prêtent, des contaminations nouvelles. Le caractère essentiel des accès que peuvent présenter des sujets prémunis réinoculés est d'être moins graves que l'accès de primo-infection: dans le paludisme l'accès pernicieux est, sauf de rarissimes exceptions, un accès de première invasion. C'est ce qui explique la résistance relative opposée aux réinfections par les Indigènes et les vieux colons d'une région paludéenne, qui gardent une infection latente depuis leur enfance. Très souvent l'accès du prémuni est purement parasitaire; aucun signe clinique ne le trahit et il resterait occulte si l'examen microscopique ne révélait pas la pullulation microbienne.

En résumé, un caractère commun des «accès de prémunis», quelle que soit leur origine, est d'être, presque toujours, des «accès avortés».

2. — Sujet réinoculé après la fin du stade latent métacritique, c'est-à-dire lorsqu'il est déparasité.

Dès que cesse l'infection latente, le sujet redevient sensible à une nouvelle contamination.

Tels sont les deux caractères de la prémunition: immunité relative, corrélative de l'infection latente, sensibilité entière revenue dès la guérison parasitaire.

Virus-vaccins prémunissants. — Les virus tués ne vaccinent pas contre les paludismes. Seuls les virus-vaccins vivants peuvent prémunir contre les Plasmodies.

Le meilleur procédé de vaccination consiste à pratiquer une inoculation virulente suivie, dès l'apparition dans le sang des premiers parasites, d'une injection de médicament antipaludique, qui fait avorter l'accès aigu, mais laisse le sujet en état d'infection latente.

(P. relictum). — Deux autres procédés nous ont donné quelques succès, mais ils n'ont pas d'intérêt pratique: l'inoculation à des Canaris de sporozoïtes extraits des glandes salivaires de Moustiques, et vieillis: conservés *in vitro* de 24 à 48 heures. — L'inoculation de Plasmodies prélevées pendant la période d'incubation de l'infection chez l'Oiseau.

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* *

En conclusion, on peut rappeler ce qu'a écrit Pasteur, en avril 1881: «Pour préserver des atteintes des maladies virulentes, il n'est pas indispensable de placer l'économie dans des conditions d'immunité absolue, mais seulement relative» [1].

(La bibliographie concernant cette Communication sera donnée dans les Archives de l'Institut Pasteur d'Algérie, *t. 37, mars 1959, pp. 1-52).*

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[1] PASTEUR — *Oeuvres*, **7**, voir p. 59, Masson, édit., Paris.

STAINING *PLASMODIUM BERGHEI* WITH FLUORESCEIN-LABELLED ANTIBODIES

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We appreciate this opportunity to show a few slides of the staining of malarial parasites by fluorescein-labelled antibodies. This work was accomplished only within the past couple of weeks at the Communicable Disease Center in Atlanta, Georgia (U. S. A.).

The globulin portions of serum from rats which were immune to superinfection with *Plasmodium berghei* were conjugated with fluorescein isocyanate by the method of Coons and Kaplan (1950) as modified by Goldman and Carver (1957). Thin films of rat blood heavily parasitized with *P. berghei* were air dried and fixed in methyl alcohol. They were then covered with a 1:4 dilution of fluorescent antibody globulin for one hour at 37° C. After washing, the films were mounted in glycerine-saline and examined with a fluorescence microscope.

Parasites became brilliantly fluorescent within the red blood cells which were visible but not stained in a specific manner with the fluorescent antibody solution (Fig. 1). It appears that the cytoplasm of the parasite takes the stain and not the nucleus. As yet, we have not had the opportunity to determine in detail the specificity of the observed reaction. We know that the parasites are not auto-fluorescent, and do not stain with fluorescein alone, nor with several fluorescein-labelled antisera against bacterial agents.

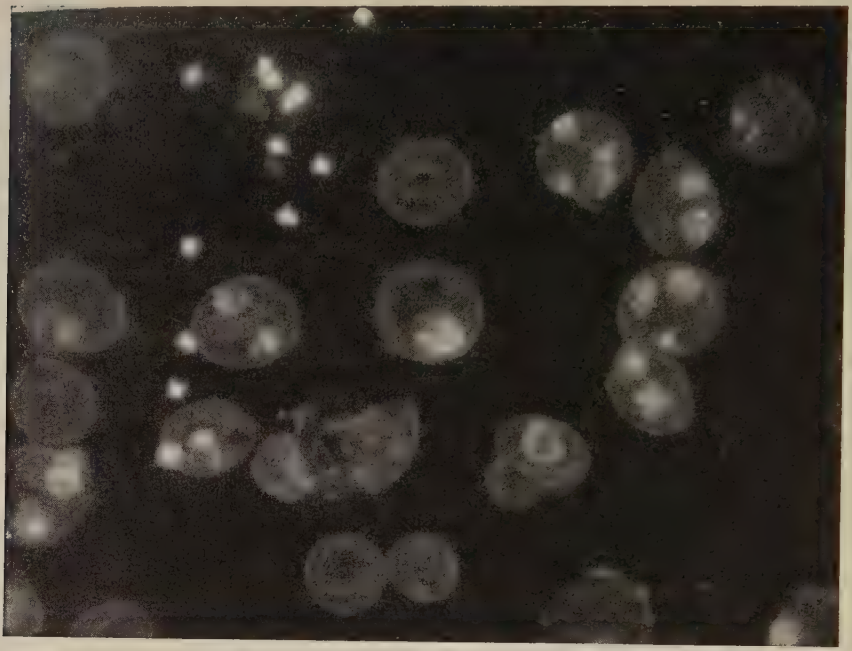

Fig. 1 — *P. berghei* stained with fluorescein-labelled antibodies. Note stained trophozoites within rat erythrocytes and extra-cellular merozoites

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1 — COONS, A. H., and KAPLAN, M. H. — «Localization of antigen in tissue cells. II — Improvements in a method for the detection of antigen by means of fluorescent antibody», *J. Exper. Med.*, **91**: 1-13, 1950.

2 — GOLDMAN, M., and CARVER, R. K. — «Preserving fluorescein isocyanate for simplified preparation of fluorescent antibody», *Science*, **126** (3278): 839-840, 1957.

GENERAL DISCUSSION

Dr. N. **Swellengrebel** (Netherlands) — Speaker reminds the audience of a publication of 26 years ago by Professor Schüffner, Dr. Annecke, Dr. de Meillon and himself, in which they compared the response to hyperendemic malaria conditions of (1) the population of certains parts of Sumatra (S. E. Asia) and (2) of certain parts of S. Africa. To put the outcome a few words: the S. African negroes had a high parasitemia and a high tolerance, the Malayans a lower parasitemia and a lower tolerance. The authores explained this as a racial character of the African race. Bagster Wilson later on explained it as the effect of amore intense infection due to the African *A. gambiae*. Still later the speaker was unable to agree to this.

The resistance to malaria infection related to the sickle cell trait did not — at first — bring a solution, because it was supposed to *prevent* infection.

If this were so it could never explain the high degree of tolerance (*premunition*) characteristic of the African race.

However, a recent publication by Allison seems to provide a satisfactory solution. He showed that the sickle cell trait does *not* prevent infection but inhibits it in infants and so allows them to bridge over the critical period during which their tolerance is still insufficiently developed.

3RD SESSION: *Wednesday, September 10th, 11.00 to 12.30 a.m. Room D*

The meeting was held under the Chairmanship of Dr. W. Kikuth.

The Rapporteur was Dr. Clay G. Huff and the Secretary was Dr. José S. Queirós.

The following papers were presented and discussed:

SOME ASPECTS OF THE NUTRITION OF MALARIA PARASITES

WILLIAM TRAGER (Co-rapporteur)

To be presented before the Sixth International Congresses
on Tropical Medicine and Malaria

Erythrocytic malaria parasites, like other intracellular parasites, obtain nutrients from both inside and outside their host cell. It is important to remember that materials utilized from outside the host cell can reach the parasite only by way of the host cell. Hence in order to study the nutritional requirements of such an intracellular parasite, as distinguished from the requirements of the complex of host cell plus parasite, it is necessary to maintain the parasite extracellularly *in vitro* under conditions which support at least a limited amount of growth. Such conditions have been developed for the avian malaria parasite *Plasmodium lophurae,* a species whose erythrocytic stages develop readily in chickens and ducks.

P. lophurae, and the erythrocytic stages of other malaria parasites as well, are intracellular phagotrophs. Electron microscopy of thin sections of duck red blood cells infected with *P. lophurae* shows how the parasite ingests portions of red cell cytoplasm into food vacuoles within which the hemoglobin is digested. The hemoglobin obviously serves as a bulk source of nitrogen, but all the details of aminoacid requirements remain unknown. What else do the parasites obtain from the host cell?

In experiments attempting to answer this question, the parasites

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were removed from their host cells by means of a hemolytic serum and incubated extracellularly at 40° C in flasks of various culture media. Work already published has shown that under these conditions the extracellular survival and development of *P. lophurae* are favored particularly by a concentrated duck erythrocyte extract. Furthermore, the organisms have been shown to require external sources of coenzyme I, adenosinetriphosphate and coenzyme A, as well as of pyruvate and malate. For best results the red cell extract medium containing all these supplements must be supplied fresh at intervals of 12 hours. Development occurs and virtually all the parasites remain in good condition through the 3rd day of culture, the day of preparation being considered as day 0. By the 4th day, a progressive degeneration begins, although infectivity for ducks has been demonstrated even after 5 days *in vitro*. More recently, two lines of investigation have been pursued. One consists of attempting to improve the culture medium for *P. lophurae* so as to prolong the period of extracellular development *in vitro*. The other consists of attempting to gain some knowledge of the nature of the materials in red cell extract, other than hemoglobin, which are essential for even a 1-day period of extracellular development.

In attempts to prolong the period of extracellular growth, it was found that the addition of folinic acid at a concentration of 0.013 mM improved the survival evident on the 4th day of incubation. The folinic acid had no effect on the increase in proportion of multinucleate parasites which occurred during the first day of incubation, and likewise no effect on the small proportion of degenerate parasites present after 3 days. But on the 4th day, some interesting differences appeared. In some experiments only half as many degenerate parasites could be seen in stained films from cultures with folinic acid as in those from cultures without it (all the flasks containing folic acid at the low concentration of 0.01 μg per ml). In other experiments the results were more variable, but always the best cultures would be among the flasks with added folinic acid. The addition of folic acid at a comparably high concentration did not have the favorable effect observed with folinic acid. This favorable effect of folinic acid was evident not only in stained films but also in fresh preparations examined with the phase contrast microscope. Most of the parasites had cytoplasm of an even medium-bright appearance. Clusters of merozoites were present, showing that reproduction was still going on.

Although no effect of folic acid on extracellular *P. lophurae* could be found, an effect of this material has been shown for malaria parasites developing intracellularly in suspensions of intact red cells, that is, under conditions comparable to the growth of a virus or rickettsia in tissue culture. Glenn and Manwell observed such an effect with an avian malaria parasite, and I found it in an experiment with the human *P. falciparum*. Heparinized blood from a paretic with a fairly heavy infection of *falciparum* was sent me through the kindness of Dr. Martin D. Young. The cells were diluted with a mixture of normal human blood and an appropriate culture medium. During the first day of incubation the rings present in the original blood developed into large multinucleate parasites. These had a better morphological appearance in the flasks with a high concentration of folic acid (1.7 µg per ml) than in those with a low concentration (0.01 µg per ml). After 48 hours the difference was more striking. At this time the cycle of the parasites had been completed and young rings again predominated. The number of rings of normal appearance was far greater in the flasks with high folic acid, and correspondingly the number of degenerate parasites was far smaller. It appears as if the host cell-parasite complex requires folic acid, whereas the parasite itself requires folinic acid or possibly some further coenzyme form of this material.

In experiments designed to get some idea as to the nature of the materials in red cell extract, other than hemoglobin, which are essential for even brief survival of the extracellular parasites, an 18-hour assay was used. This was based on the findings that: (1) in flasks inoculated with a purified suspension of extracellular parasites consisting chiefly of uninucleate trophozoites there occurred an increase in proportion of multinucleate forms; (2) this increase was roughly proportional to the concentration of the red cell extract. Each experiment included two kinds of control-one with a minimal concentration of red cell extract introduced with the inoculum of parasites, the other with half — or full — strength extract to provide optimal conditions. If a material under test supported the appearance of more multinucleate forms (chiefly forms with 2-4 nuclei) than appeared in the negative controls, then the material could be considered as having activity of the type found in the red cell extract. The *pH* of the medium and all the known supplements were kept uniform throughout. Under such conditions it was found that certain yeast protein preparations high in hexokinase activity could partially replace red cell extract. The active material was non-dialyzable and perhaps was a protein. It is distinct from hexokinase, since a hexokinase preparation whose enzymatic activity was lost by keeping it at 27° C for 1 day still had activity for the malaria parasites.

Direct fractionation of the erythrocyte extract was attempted by zone electrophoresis on starch. First a number of preliminary experiments had to be done. It was necessary to prepare the red cell extract not in the complete nutrient medium but in water or dilute buffer, and then to mix the extract and fractions from it with an appropriate volume of more concentrated medium to restore isotonicity. Fractions obtained from the starch block had to be sterilized as relatively dilute solutions by filtration through bacteriological filters and subsequently concentrated under sterile conditions. Such concentration was accomplished by dialysis of the solutions in sterile cellophane bags against 20 % polyvinylpyrrolidone at a temperature of 1° C. From such preliminary experiments it was found that the increase in multinucleate forms was as great in medium prepared from aqueous extract mixed with concentrated diluent to give half strength red cell extract, as in red cell extract made by the standard method previously used (direct extraction of frozen-thawed cells in isotonic diluent). Concentration by dialysis against polyvinylpyrrolidone had no deleterious effect, proving that the factors under study were non-dialyzable. Storage of the aqueous red cell extract for five days at 1° or at 20° C had no effect, but 5 days at 27° did decrease its efficacy.

The first starch electrophoresis experiments were done with duck red cell extract made in 0.05 M phosphate buffer of *pH* 7.3 and applied to a starch block prepared in the same buffer. The hemoglobins (of which there were two) migrated to the left toward the cathode, and activity was found with the hemoglobin fraction, or, in one experiment, with colorless material just left of the origin. When buffer of *pH* 7.5 was used the hemoglobin still migrated to the cathode, but activity for the extracellular parasites was present in a region going right from the origin. For these experiments relatively large sections of the starch block were cut out, mixed with appropriate volumes of buffer and the starch removed by filtration. After sterilization through porcelain filters the solutions were concentrated by dialysis against polyvinylpyrrolidone. They were finally made up with buffer and hypertonic nutrient solution to give an isotonic solution theoretically equivalent, if full activity had been retained, to a half-strength red cell extract. Three different concentrations of red cell extract were usually included as controls. The hemoglobin fractions obtained at *pH* 7.5 were not only inactive but somewhat toxic, perhaps as a result of the visible amounts of methemoglobin which formed at this *pH*. The significant finding was that a colorless fraction having less than 1 % as much protein as red cell extract had about half as much activity. This activity appeared not to move far in the electric field. Moreover, it could not be recovered in segments of the starch block less than 4 cm wide. Either the material spreads somewhat, or perhaps two materials are concerned.

Obviously, a great deal remains to be done before this non-dialyzable malarial growth factor can be characterized even in a general way. In our present state of ignorance, however, we are free to speculate that if this factor is a protein it might be an enzyme of the host cell which the malaria parasite needs but does not make itself.

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A COMPARATIVE STUDY OF THE TISSUE PHASE OF SEVEN SPECIES OF MALARIA PARASITES OF MAN AND APES

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When Laveran announced in 1880 the discovery of intracorpuscular bodies in the blood of soldiers suffering from malaria few people were willing to accept these bodies as being the cause of the disease. It required the careful work of Golgi (1889) which demonstrated the details of the blood cycle, and the invention of a double stain by Romanowsky (1891) finally to convince everyone of the true existence of malaria parasites. But once convinced they began, not only to produce lurid pictures of the organisms accompanied by dramatic texts which today so copiously illustrate our textbooks, but to create new species of parasites in many branches of the animal kingdom. Most writers became so obsessed by the ring-schizont-gametocyte picture in the peripheral blood that they lost sight of the adult form of the organism in the mosquito or the more fundamental stages in the tissues of the vertebrate host. Thus the descriptions of the different species today are practically confined to the blood stages as seen in dried films, on which their taxonomic status is entirely based. Unfortunately the sporogonic forms of the parasites exhibit few or inconspicuous characters available for differentiating the species, but the pre-erythrocytic schizonts on the other hand show features constant in production, striking in morphology, and with as regular a time-table as the tertian or quartan cycles of the blood schizonts. It is the purpose of this paper to compare the tissue forms of seven species of *Plasmodium* of primates, and to show how valuable they are for the classification of these organisms. It is not suggested that one should use these characters for the routine diagnosis of malaria parasites, obviously quite an impracticable procedure, but that one should use them for visualising an organism; thus one should think of *Plasmodium falciparum* more as a rapidly growing pleomorphic

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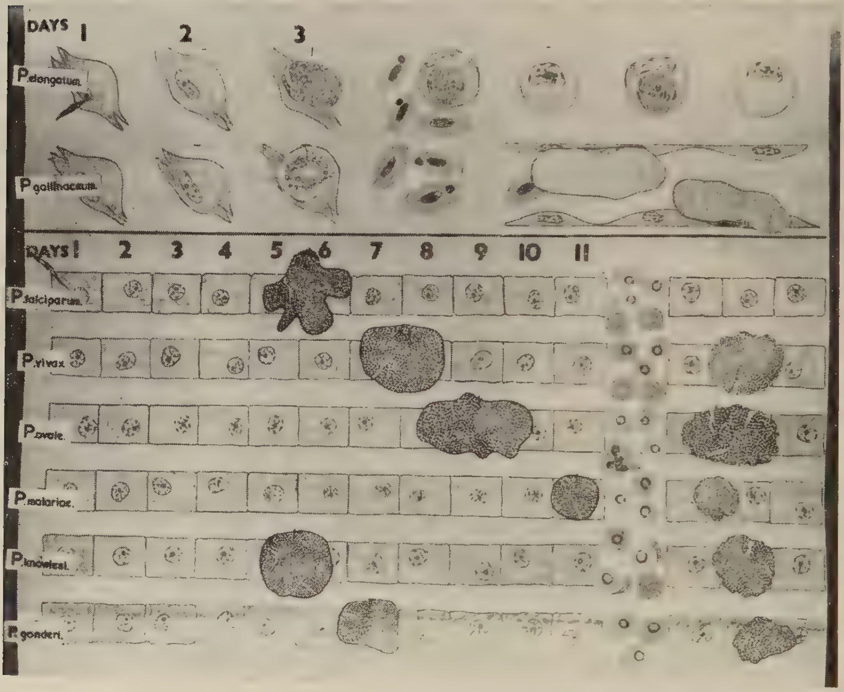
schizont with 50,000 tiny nuclei, living for a single generation only in the liver, rather than as small erythrocytic schizonts blocking the brain capillaries of the host and terminating their own and their host's lives.

The nature of pre-erythrocytic schizogony is now known in 7 species of primate *Plasmodium* — *P. cynomolgi* (Shortt, Garnham and Malamos, 1948), *P. vivax* (Shortt, Garnham *et al.*, 1948), *P. falciparum* (Shortt *et al.*, 1951), *P. inui* (Garnham, 1951), *P. ovale* (Garnham *et al.*, 1955), *P. knowlesi* (Garnham *et al.*, 1957) and *P. gonderi* (Garnham *et al.*, 1958). *P. cynomolgi* and *P. vivax* are the simian and human representatives respectively of benign tertian malaria and are so closely allied that few differentiating features exist; the descriptions below apply particularly to the former which has been more extensively studied.



Pre-erythrocytic schizogony is as integral a part of the life cycle of *Plasmodium* as any of the better known stages; it appears to take place, in the parasites under discussion, solely in the parenchyma cells of the liver where it occurs as a single generation beginning with the sporozoite and ending in the rupture of the schizont and the discharge of thousands of merozoites into the blood stream. In most species a few merozoites re-enter parenchyma cells to initiate the exoerythrocytic cycle. purposes are as follow:

The characters of the tissue stages of these species for taxonomic purposes are as follow:

1. Duration of pre-erythrocytic schizogony,
2. Presence or absence of exoerythrocytic cycle.
3. Size and shape of schizont,
4. Size and number of merozoites,
5. Type of nucleus,
6. Type of cytoplasm.

DURATION OF PRE-ERYTHROCYTIC SCHIZOGONY

This stage lasts from the introduction of the sporozoite into the vertebrate host until rupture of the mature schizont, and its exact duration depends upon how soon the sporozoites are able to penetrate the parenchyma cells of the liver; probably not more than an hour or so is involved because even the introduction of the sporozoites by mosquito bites (as in the experiments of Fairley, 1947), when the parasite has to overcome a number of obstacles before reaching the blood stream, is followed by a very short period during which the sporozoites circulate in the blood, or, in other words, before they are taken up by the liver. But just as the cycle of schizogony in the blood is not absolutely tertian or quartan, so in the tissue stages, there are some rapid developers as well as laggards, and a few schizonts may rupture some hours earlier (or later) than the main bulk. For the purpose of classification then, precocious forms may be ignored (though their existence will explain the unusually short pre-patent periods occasionally reported), and the time when the main burst of schizonts occurs is used to fix this criterion.

The length of pre-erythrocytic schizogony may be ascertained either by watching the blood carefully for the first appearance of merozoites after infection with a maximum number of viable sporozoites, or better by direct observations of mature forms in sections of liver.

P. knowlesi has the shortest cycle of any of the primate malaria parasites, viz. about 5 ½ days.

P. falciparum is almost equally quick in its tissue cycle, viz. about 5 ½ days, but Shute and the Italian workers (Monaldi and Raffaele, 1953) have reported pre-patent periods of 5 days or less in different strains. Thus Shute (personal communication) found parasites as early as the fourth day after intravenous inoculation of sporozoites derived from a Rumanian strain. *P. falciparum* grows rapidly to a large size, pushing its way amongst the neighbouring liver cells, and it is easy to believe that a few parasites might reach maturity precociously under these circumstances. Bray (1958) found that the pre-erythrocytic stage of this parasite in the chimpanzee was extended to 6 days.

P. gonderi takes 7 ¾ days to attain maturity.

P. cynomolgi has been studied widely, principally in the strain isolated by Sinton and Mulligan (1933). This strain shows a duration of pre-erythrocytic schizogony of about 8 days. Hawking, Perry and Thurston (1948) noted carefully the exact duration of the pre-patent period of this strain of *P. cynomolgi* and found that it was 3 hours short of 8 days, and this is the period generally noted by workers at the London School of Hygiene and Tropical Medicine for the same strain. A new strain was obtained from Dr. J. F. B. Edeson in a Kra monkey from Malaya in 1957, and close observations on this strain showed that the blood was invaded as early as 7 days. Without a large series of experiments, it would be impossible to be sure if this represents a true strain difference; in the meantime, the length of pre-erythrocytic schizogony for this species may be taken as eight days. The same figure is true for *P. vivax,* though Bray (1957-*a*) using the chimpanzee as the vertebrate host obtained a figure of 7 ¼ days, for the same Madagascar strain of the parasite.

P. ovale exhibits a clear-cut period of 9 days for the duration of pre-erythrocytic schizogony. It is interesting to note that two strains of widely different origin (Liberian and Philippines) were shown by Jeffery, Wilcox and Young (1955) to have pre-patent periods of less than a day's difference. In the chimpanzee, also, the cycle is exactly 9 days (Bray, 1957-*b*).

P. inui in my original observations (Garnham, 1951) was thought to have a pre-patent period of 12 days. Later, unpublished work on the same strain showed that a more precise figure was 11 days, while recent experiments of Mohuiddin (1957) on a new strain have confirmed the latter figure.

PRESENCE OR ABSENCE OF AN EXOERYTHROCYTIC CYCLE

Indirect evidence denoting the persistence of liver forms comes from two sources: (1) the ability of good schizonticides like quinine or chloroquin to cure radically certain types of malaria (*P. falciparum*) but not others and (2) the existence of long term relapses with a complete absence of parasitaemia in between each relapse (in infections with all parasites except *P. falciparum*).

Direct evidence is hard to come by; the exoerythrocytic forms are anyhow scanty and difficult to demonstrate, while to confirm their total absence, i. e. to prove a negative, is really impossible. A persisting cycle might be assumed to occur if second generation forms could be found in an experimental infection — and these have often been seen in *P. cynomolgi;* on the other hand, Bray (1958) completely failed to find second generation forms of *P. falciparum* in artificially inoculated chimpanzees.

True relapse bodies have only been demonstrated in two species, *P. cynomolgi* by Shortt and Garnham (1948) and Garnham and Bray (1956), and *P. vivax* by Rodhain (1956). Their morphological characters are little different from those of the pre-erythrocytic schizonts; the size is the same and the nuclear structure and cytoplasm show no apparent difference, but the contour tends to be slightly convoluted or wrinkled. There is little doubt that exoerythrocytic schizogony exists in *P. malariae* and other quartan parasites, and in *P. ovale*. It may be absent in *P. gonderi* which is characterized by a never-ending parasitaemia. It probably occurs in *P. knowlesi* and Edeson (1953) has described large bodies in the liver of chronically infected monkeys which he thinks may be exoerythrocytic schizonts.

SIZE AND SHAPE OF SCHIZONT

These characters are unfortunately not absolutely constant; even the most uniform parasite — *P. inui* — may rarely show irregularities of contour, while *P. cynomolgi* frequently assumes a giant form. Provided enough schizonts are available for examination, size and shape however provide a useful guide to diagnosis.

P. knowlesi is usually smooth, unlobulated and subspherical in contour, measuring 25 μ at 3 ¾ days and 40 μ at maturity.

P. falciparum is often slightly irregular in shape even as early as 4 days when it is about 30 μ in diameter; at maturity it throws out various lobose projections, which in section often appear as separate parasites. At maturity it may be 60 μ or more in length.

P. gonderi is a small parasite of regular contour, which at maturity is rather less than 30 μ in diameter.

P. cynomolgi commences its development in the liver as a round or oval body only 2 μ in size, which in a week reaches nearly 40 μ. Its contour is smooth and spherical or oval, except when the presence of a large vacuole causes indentation on the surface. Some forms continue to grow after the normal length of the cycle, and may reach a diameter of over 100 μ (Bray, 1957-*c*).

P. vivax tends to be slightly larger than the preceding species and at maturity reaches a diameter of about 50 μ.

P. ovale produces the largest schizonts of any of these species; they are 85 μ or more in length and usually have an irregular lobulated contour. At 7 days, the irregularity is less marked and the parasite measures about 33 μ.

SIZE AND NUMBER OF MEROZOITES

The number of merozoites in any schizont is dependent upon its actual size, which varies considerably in the same species and infection; it is difficult to estimate with any accuracy, and the numbers give in the table are only approximate. The size, however, is an important feature and there is an obvious difference between the large merozoites of *P. ovale* and the tiny ones of *P. falciparum*. The sizes are show in the table.

TYPE OF NUCLEUS

The nuclei of the seven species here described show profound differences which possibly represent fundamental characters. The Feulgen reaction and fluorescent staining confirm these points. The parasites seem to fall into 2 groups: (1) *P. cynomolgi* and *P. vivax* have a «simple» type of nucleus which until very late in development is practically Feulgen negative and (2) *P. falciparum, knowlesi, gonderi, inui*, and *ovale* have a more complex nucleus which quite early is strongly Feulgen positive.

P. cynomolgi and *P. vivax* nuclei throughout their development appear as solid undifferentiated structures, which, particularly between the sixth and seventh days, are elongated into a bar form. The nuclei are scattered rather sparsely throughout the cytoplasm and show no localisation to any particular zone.

P. inui possesses nuclei which are again undifferentiated in internal structure, but they do not assume the bar formation characteristic of the preceding species, while like the remaining ones of this group they early become Feulgen positive. Their distribution in the schizont is however striking: between the ninth and tenth day, there is a pallisade arrangement on the surface of the parasite; then a little later they collect in the whorls or cartwheels of the pseudocytomeres (see below).

P. falciparum has nuclei which in the younger stages are rather like those of the first group, but they are slightly larger and usually appear granular.

P. ovale differs from all the other species in the size of the nuclei; at all stages of development of the pre-erythrocytic schizont, the nuclei are very large, while at one time — about the seventh day — they form large tangential plaques 4 μ across on the surface of the parasite. Bray (1957-*b*) has shown that in exoerythrocytic schizonts of this species in the chimpanzee, the chromatin may be deposited in large masses 7 μ across; these take up a different staining reaction from the ordinary nuclei and their exact significance is unknown. The large nuclei at all stages of growth consist of a number of granules, usually about 6. Towards the end of schizogony some reduction in the size of the nucleus occurs.

P. gonderi also shows nuclei of the granular form — 3 or 4 granules lying in a matrix of paler staining material; their size is fairly large and on the seventh day is double that of the nuclei of *P. cynomolgi*. They differ from the latter also in being much more closely packed.

P. knowlesi has a nuclear structure which reaches the greatest degree of complexity. Firstly the nuclei are nearly always in the form of a cluster of 4 deeply staining dots which are Feulgen positive from an early age. The formation is so clear in this species, that it can easily be interpreted as some step in mitosis, e. g. suspended telophase. Secondly the nucleous and cytoplasm on the 3rd and 4th days are often dissociated from each other, while later a gradual seeding of the latter by the former takes place. Apart from this discontinuity there is no special localisation of nuclei in the pre-erythrocytic schizonts of *P. knowlesi*.

TYPE OF CYTOPLASM

The morphology of these forms of primate malaria is largely based on material which has been fixed in Carnoy's fluid. This is excellent for most purposes, but one suspects that it may have a distorting action on the cytoplasm of the parasites, and direct comparison of tissue fixed in Zenker's, Schaudinn's formol-saline and Carnoy's fluid showed that the uniform, slightly granular appearance of the cytoplasm seen after fixation with the first three was lost in the Carnoy-fixed, where contraction, condensation and vacuolation became pronounced. In spite of this defect, however, Carnoy-fixed material shows the greatest colour contrasts and produces a vivid blue colour with Giemsa staining never seen with the other fixatives. For these reasons, one must interpret cautiously some of the appearances described below.

The cytoplasm of every schizont is enclosed in a limiting membrane which is usually difficult to see unless the section is much overstained. In *P. ovale*, the membrane, or periplast, is more easily visible; it is often discontinuous.

P. cynomolgi and *P. vivax* have a granular cytoplasm, fine or coarse according to the fixative used, but plentiful in amount. These parasites show two special features: (1) the presence of basophilic aggregations, which Das Gupta (1958) and others have shown to consist of ribonucleic acid, and (2) one or more large vacuoles which contain an amorphous material of unknown composition. The vacuoles are only seen between the 6th and 7th days and disappear at maturity. The cytoplasmic aggregations occur slightly earlier but are absent in both the young and mature forms.

P. inui show a feature of the cytoplasm which is most marked in this slowly growing species but is probably present to a greater or lesser extent in the other species. This is the formation of «pseudocytomeres» — the cytoplasm condenses into hollow spheres which remain connected to each other by incomplete bridges, while the nuclei become studded in the walls, to give a cartwheel effect on section. Completely discrete cytomeres are rarely noted. This appearance is best seen towards the end of schizogony; earlier the cytoplasm is characterized by its tenuous nature, and on the ninth day is in little more than threads.

P. knowlesi shows a remarkable dissociation of cytoplasm and nuclei, first seen on the third day, when flocculi of cytoplasm rarely contain any nuclear material; the next day, the flocculi are larger and a few nuclei are drawn into them; later the seeding is heavier and it is possible that the large cytoplasmic masses split up into smaller pieces, each containing 4 to 6 nuclei. The flocculi are composed partly of ribonucleic acid and partly of an unknown substance soluble in warm water.

P. falciparum has a finely granular, uniform cytoplasm in the earlier stages; towards the end of schizogony, it tends to break up into small masses, divided by clefts, which are suggestive of pseudocytomere formation.

P. gonderi shows finely granular cytoplasm without vacuoles and without basophilic clumps as a rule. Occasionally clefts appear in the cytoplasm, giving rise to pseudocytomeres of an unusual type.

P. ovale has granular cytoplasm in the young form, which becomes increasingly tenuous, so that by the seventh day it forms a web throughout the schizont with the nuclei as nodes; with Carnoy fixation the web collapses and the nuclei collect like a heap of pebbles in the centre of the parasite. Such at least is the appearance of sections of infected chimpanzee's liver kindly given to the writer by Dr. Bray. By the eighth or ninth day, the cytoplasm increases in amount and frequently shows ill-defined whorls or loops, indicating the formation of pseudocytomeres.

CONSTANCY OF THE MORPHOLOGY OF THE TISSUE FORMS

The preceding section, which is summarised in the table, demonstrates the highly characteristic features exhibited by 7 species of primate malaria parasites. Although slight variations in size, shape and rate of growth of the schizonts occur, differentiating features remain clear-cut. It is uncertain, however, how strains of a single parasite behave, though a few observations tend to confirm the essential similarity of the pre-erythrocytic cycle within a species. Thus Jeffery *et al.* (1952) using a Panama strain of *P. falciparum* demonstrated the existence of a pre-erythrocytic cycle similar to that described by Shortt *et al.* (1951) based on a Rumanian strain. On the other hand, there are curious differences in the prepatent period of strains of *P. falciparum* (see above). Different strain of *P. vivax, P. inui* and *P. cynomolgi* behave alike, though in the last a recently isolated strain from Malaya has shown a prepatent period nearly a day less than that of the old strains.

The effect of change of species of the host on pre-erythrocytic schizogony has again been little investigated. Bray's experiments with chimpanzees and human malaria parasites have demonstrated their identical behaviour in the two hosts, with a single exception: *P. falciparum* takes a day longer to attain maturity in the ape-though this may have been due to a change in strain of parasite (Liberian instead of Rumanian).

The writer has recently completed a series of experiments designed to observe the behaviour of *P. cynomolgi* in 4 different kinds of monkey. A new strain of *P. cynomolgi*[1] isolated from a *Macaca irus* from Malaya was used, and from it about 500 *Anopheles maculipennis atroparvus* and a few *A. aztecus* were infected (100 per cent). 400 pairs of salivary glands were dissected out, and were inoculated intravenously into 4 monkeys, the amount of inoculum being roughly proportional to the weight of animal. Biopsies of liver were taken from each animal 7 days later and the incidence and appearance of pre-erythrocytic schizogony were compared with the following results:

Macaca mulatta (half-grown rhesus monkey). The prepatent period occupied 7 × 24 hours (i. e. exactly 7 days). 55 pre-erythrocytic schizonts per 100 sq. mm. were found in the sections of liver, the maximum size of each schizont being 35 μ.

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[1] Now designated *P. cynomolgi bastianellii* (note added in 1962).

Papio papio (baboon aged about 1 year). The prepatent period was again exactly 7 days, while 100 schizonts per 100 sq. mm. were found in the liver sections, the largest of which was 32 μ.

Cebus apella (adult capuchin from Brazil). No parasites were detected in the blood at 7 days or later, but pre-erythrocytic schizonts were numerous in the liver — 125 per 100 mm², the maximum size being 33 μ.

Macaca irus (Full grown Kra monkey from Malaya, originally showing a natural infection of *P. cynomolgi* and later a persistent *P. inui*). *P. inui* parasites were fairly numerous in the blood throughout the experiment, but a new infection of *P. cynomolgi* was never confirmed because the animal died 2 days after the biopsy. The liver showed pre-erythrocytic schizonts of abnormal morphology at the rate of ½ per 100 sq. mm., and measuring less than 20 μ in diameter.

It is probably best to ignore the results in the last monkey — which was neither a clean nor a healthy animal — but the remaining three provide an interesting picture. The schizonts in these animals were approximately in the same density (no exact quantitative results can be hoped for in work of this kind when an unknown number of sporozoites reaches the liver), and all had a similar size and structure. Few vacuoles were present because the parasites were approaching maturity, in fact merozoite formation was beginning in many of them; for the same reason bar-shaped nuclei were rare, that stage being already past. The duration of pre-erythrocytic schizogony in this new strain was confirmed as lasting only 7 days, a day shorter than usual. The baboon is seen to behave just like the rhesus, but the New World monkey reacted differently: the tissue stage of *P. cynomolgi* progressed normally, but parasitaemia failed to ensue — a result exactly analogous to the behaviour of *P. vivax* or *P. falciparum* in the chimpanzee, where tissue forms occur normally but erythrocytic development is inhibited (in animals with an intact spleen). The New and Old World monkeys separated very far back in geological time and this result is therefore not unexpected; it suggests that the chasm between them may be of the same degree as that separating the chimpanzee and man. The employment of such a test might prove useful in the determination of relationships of the primates in general.

An unpublished experiment on similar lines was carried out under my supervision by Dr. Thierry Freyvogel (Institute of Tropical Medicine.

Basle) in 1955, when a rhesus monkey and a *Cercopithecus aethiops* were inoculated with equal quantities of sporozoites of the Rockefeller strain of *P. cynomolgi,* and the incidence of pre-erythrocytic schizonts on the seventh day was determined. About 4 schizonts per 30 sq. mm. were found in each, but the average diameter was 25 per cent less in the schizonts in the African monkey.

Strain of parasite and species of host (within limits) are therefore seen to have little influence on the essential characters of the tissue forms.

The effect of immunity has been studied by Garnham & Bray (1956) who concluded that acquired immunity neither influenced the number nor the morphology of pre-erythrocytic schizonts of *P. cynomolgi,* but they observed that it stimulated early exoerythrocytic schizogony which was much more prolific in immune monkeys than in susceptible ones.

TAXONOMIC CONSIDERATIONS AND CONCLUSIONS

When a living creature is described, it is the fully grown mature form which normally receives most attention; not the bird's egg or the tadpole, nor the spermatozoon or embryo, but the adult. Yet in the case of the malaria parasites, descriptions have been practically limited to the transient stages occurring in the blood instead of the sexually mature forms in the mosquito or the more fundamental and much more productive schizonts found in the tissues. The reason for this is of course because the blood forms are the ones easily seen and are of practical value to man. In this paper, I hope to have corrected this irrational approach and to have shown that the appearance and behaviour of the tissue stages of the parasites are at least as characteristic as the stages found in the blood and probably more significant taxonomically. Thus *P. ovale* is now seen to possess as highly characteristic tissue forms as any of the rest, and is not, as was once thought, a «sort of cross between quartan and benign tertian malaria»; while *P. gonderi* is clearly a distinct species, quite outside the «benign tertian» group to which it was originally thought to belong. The absence of exoerythrocytic schizogony in *P. falciparum* provides an additional reason for placing this parasite in a separate genus — *Laverania* (as recommended by Bray, 1958). The discovery of the tissue stages of other species of primate malaria will undoubtedly help in their classification; there is little reason to doubt that *P. schwetzi* will be found to resemble *P. vivaz* and *P. reichenowi*, *P. falciparum;* probably the quartan parasites *P. malariae*, *P. brasilianum* and *P. hylobati* will resemble *P. inui*; but *P. simium* may well be found to belong not to the «benign tertian» group, but to some other.

Five years ago (Garnham , 1953), I made a plea to the 5th International Congress of Tropical Medicine and Malaria for an extended classification of the malaria parasites. The evidence that has accumulated in the meantime has substantiated the generic difference between the mammalian and the avian parasites, and the re-establishment of old genera is gradually being effected today. A special diagram fitted with slits and moving cards (based on lecture diagrams of Sonneborn used for illustrating the genetics of *Paramecium*) has been prepared to illustrate the main features (see p. 68).

It is the purpose of the present paper, however, not to reclassify these organisms, but to stress the need of an alteration of outlook: to think of these species as coccidian parasites of the liver of primates and not merely in their parvenu form in the blood stream.

May I end by saying what a great privilege it is for me to present a paper on this subject at a meeting, which has for its Chairman Col. H. E. Shortt, whose fundamental work on the problem is known to everyone, for its Rapporteur Dr. Clay Huff, who has elucidated so many of the cycles of the bird parasites, and amongst its audience Prof. G. Raffaele, the first person to demonstrate exoerythrocytic schizogony in malaria?

Differential characters of the tissue phase of primate malaria parasites

Species of parasite	Length of pre-erythrocytic cycle	Approximate size of mature schizont	Approximate number of merozoites	Size of merozoites	Special features	Existence of exoerythrocytic cycle
P. *cynomolgi*	7-8 days	40 μ	under 10,000	1.2 μ	vacuoles	yes
P. *vivax*	8 days	45 μ	over 10,000	1.2 μ	vacuoles	yes
P. *falciparum*	5 ½ days	60 μ	40,000	0.7 μ	small nuclei	improbable
P. ***inui*** **(quartan)** ...	11 days	25 μ	2,000	1.0 μ	cytomeres	probable
P. *ovale*	9 days	70 μ	15,000	1.8 μ	large nuclei	probable
P. ***knowlesi***	5 ½ days	40 μ	?	1.2 μ	flocculi	probable
P. ***gonderi***	7 ¾ days	30 μ	8,000	1.0 μ	nuclei with clustered granules	probable

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STUDIES ON MALARIA IN CHIMPANZEES

VII. *The Use of the Chimpanzee in Malaria Research*[1]

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It has been known for some time due to the work of the late Prof. Jerome Rodhain that the chimpanzee is susceptible to infection with *Plasmodium malariae* of human origin and that it is also partially susceptible to infection with *P. vivax vivax*. This work has involved largely blood transmission of the parasite and told us little more than whether the human plasmodia could survive in chimpanzee erythrocytes. More recently Rodhain showed that the chimpanzee liver was susceptible to infection by sporozoites of *P. vivax vivax* and the possibilities inherent in the use of chimpanzee for the study of human malaria parasites immediately became greatly more interesting.

At the Liberian Institute of the American Foundation for Tropical Medicine it has been possible to explore this field with the minimum of difficulty. Chimpanzees have been in reasonable supply while a vigorous and successful cage colony of *Anopheles gambiae* has ensured a ready supply of vectors. Lastly the local population has been sufficiently complacent to allow an uncertain but adequate supply of parasites.

The main discovery that these conditions have allowed is the fact that the removal of the spleen renders the chimpanzee completely susceptible to all vertebrate phases of human malaria parasites. It has been possible to substitute the chimpanzee after splenectomy for man in complete studies of the human malaria parasites. The results of these investigations are set out below.

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[1] This investigation was supported by a research grant (RG-4533) from the National Institutes of Health, U. S. Public Health Service.

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 82-85, 1959

Plasmodium vivax vivax

Splenectomy of a chimpanzee infected with sporozoites of the Madagascar strain of *P. vivax* 3 months previously gave the first indication of the full possibilities inherent in the use of the chimpanzee for this type of research. After splenectomy a heavy infection appeared in the blood resulting in the production of numerous gametocytes. Prior to splenectomy no parasites had been visible. This not only indicated the susceptibility of the blood post-splenectomy but also showed that the liver must have been susceptible to the sporozoites. (This work was done just prior to Rodhain's demonstration of pre-erythrocytic forms of *P. vivax* in chimpanzee liver). *A. gambiae* were easily infected and subsequently chimpanzees and man were infected with these sporozoites resulting among other things in the establishment of the insusceptibility of Liberians to infection with *P. vivax* and the discovery of second generation exoerythrocytic schizonts of *P. vivax*.

Studies made on the two chimpanzees infected with *P. vivax* have shown that the strain behaves similarly in the splenectomized chimpanzee as it does in man; producing relapses at the 8th-10th month after infection and subsequently relapsing at irregular intervals. A continuing source of gametocytes has resulted for various studies, among others the action of drugs upon sporogony. The parasite has remained to all visible purposes typical throughout these studies. In one chimpanzee the infection has persisted with negative blood periods for 18 months.

Plasmodium ovale

Following the success with *P. vivax* it was immediately possible to repeat these studies using *P. ovale*. In this case it was established that the splenectomized chimpanzee was fully susceptible but that the whole chimpanzee eradicated the blood infection from a heavy liver infection after four generations had appeared in the blood each being less numerous than the previous one. Liver biopsies revealed first and second generation exoerythrocytic schizonts. Liver biopsy at 39 days after infection revealed an exoerythrocytic schizont probably of the fourth generation but splenectomy at this time failed to allow infection in the blood following its eradication earlier by the chimpanzee and despite the demonstration of an exoerythrocytic schizont.

Relapses and recrudescences have occurred in chimpanzees infected with sporozoites of *P. ovale* at irregular intervals. In one chimpanzee after 6 such reappearances of blood parasites the erythrocytic forms showed some changes from the accepted characters of *P. ovale*. In particular 14 merozoites were produced as a rule, the nuclei of the schizonts were small and oval host cells were uncommon. In this chimpanzee the infection persisted with apparently negative periods for 12 months.

Plasmodium malariae

This parasite has proved by far the most difficult to handle successfully using the techniques described. Although the chimpanzee is wholly susceptible to infection with *P. malariae* of human origin and although the rate of *P. malariae* in the local children is about 40 % it has been impossible to obtain a satisfactory gametocyte donor. Among the local population gametocytes have not exceeded 20 microgametocytes/mm^3 of blood [1] and infectivity to mosquitoes is uncertain; gametocyte density appearing to have only a partial significance. In splenectomized chimpanzees with both natural infections and induced blood and sporozoite infections of human origin gametocytes have been sometimes wholly absent or when present very scanty. In whole chimpanzees no infection has reached such an intensity as to produce any significant number of gametocytes.

Thus though *A. gambiae* have been infected on 16 occasions (15 from human donors, 1 from a chimpanzee donor), all from parasites of human origin, on no occasion has the gametocytaemia been sufficiently high to allow the type of investigation outlined above.

So far *P. malariae* has been transmitted successfully from man to chimpanzee 3 times by means of sporozoites and twice by means of blood. The resultant infections have been intense only after splenectomy and two such intense infections have produced no gametocytes at all. On no occasion in this series has man or mosquito been infected with

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[1] It is my personal opinion that the macrogametocyte of *P. malariae* cannot be diagnosed in routine examinations. Even in good thin films the doubt that an old trophozoite is under inspection cannot be banished with real confidence.

P. malariae of chimpanzee origin and in the light of the insusceptibility of *A. gambiae* to infection with *P. vivax schwetzi* and *Laverania reichenowi* it will be interesting to observe the susceptibility of *A. gambiae* to *P. malariae* of chimpanzee origin.

Laverania falciparum

Both a splenectomized and a whole chimpanzee have been infected with sporozoites of this parasite. In the splenectomized animal a heavy blood infection resulted showing all erythrocytic stages including schizonts and immature gametocytes in the peripheral circulation. For some unknown reason the majority of gametocytes did not come to maturity. Pre-erythrocytic schizonts were found in the liver of the whole chimpanzee but exoerythrocytic schizonts could not be found at the time of possible second generation development although similar technique revealed them in the case of *P. vivax* and *P. ovale*. It is for this reason, on the assumption of the absence of exoerythrocytic generations subsequent to the first, that this parasite has been referred to the genus *Laverania*. In the whole chimpanzee the erythrocytic stages were eliminated as they appeared from the liver.

The susceptibilities of man and chimpanzees to their malaria parasites as far as we know them are:

Parasite	Man		Chimpanzee	
	Liver	Blood	Liver	Blood
L. falciparum	A	A	A	D
P. vivax vivax	A	A	A	B
P. ovale	A	A	A	D
P. malariæ of man	C	A	C	A to B
P. malariæ of chimpanzees	E	A to B	C	A
L. reichenowi	E	F	C	A
P. vivax schwetzi	E	B	C	A

A — Complete susceptibility. B — Partial susceptibility.
C — Presumed susceptibility. D — Susceptible only after splenectomy.
E — Unknown. F — Insusceptible, splenectomy not done.

It is probable that the liver of man is susceptible to *L. reichenowi* and *P. vivax schwetzi* and equally that the blood is totally susceptible following splenectomy. Neither of these probabilities is likely to be demonstrated experimentally.

THE PRODUCTION OF DRUG RESISTANCE IN CLONES OF *PLASMODIUM GALLINACEUM*

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England

Although quinine has been used in the treatment of malaria for over 300 years, the malaria parasite has not lost its sensitivity to the drug. With the introduction of new, synthetic compounds in the treatment of the disease, however, the question arose whether drug resistance might become a problem in treatment. In 1947, Bishop & Birkett, and Williamson, Bertram & Lourie, working independently, showed that strains of *Plasmodium gallinaceum*, maintained in chicks, could be made highly resistant to proguanil (paludrine). Moreover, resistance, once it had developed, was a stable character and was retained after the strains had been transmitted through the insect vector, *Aëdes aegypti*; indeed, no reduction in the intensity of resistance was observed after one strain had been passed five times through mosquitoes and chicks without intervening drug treatment (Bishop & Birkett, 1947).

Proguanil is not the only drug which will produce resistant strains of malaria parasites; strains have been made resistant to pyrimethamine, quinine, pamaquin, chloroquine, sulphadiazine, sulphanilamide, metachloridine and pteridine compounds, but the intensity of resistance attained and the rate at which it develops varies with the compound. In addition to *P. gallinaceum*, strains of *P. lophurae*, *P. berghei*, *P. cynomolgi*, *P. knowlesi*, *P. falciparum* and *P. vivax* have been made drug resistant experimentally, and there is evidence that resistance to proguanil and pyrimethamine can develop in the course of treatment in the field.

How do these drug resistant parasites arise? There are several possibilities. They might result from an adaptation of the organism to

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the drug, in which case it might be expected that the change would be a gradual one affecting all or most of the organisms simultaneously. Or, they might arise spontaneously, by mutation, the drug merely acting as a selecting agent by killing off the more sensitive individuals, or the drug might be mutagenic, inducing the mutations. It was with the hope of throwing some light upon the means by which drug resistance arises in malaria parasites that some experiments upon the action of metachloridine (2-metanilamido-5-chloropyrimidine) upon *P. gallinaceum* were carried out. This drug was chosen because it had been found to produce resistance comparatively rapidly (Bishop & McConnachie, 1953).

Pure lines of *P. gallinaceum* were used in the experiments. These were obtained by inoculating chicks less than a week old with single erythrocytes containing single parasites, the erythrocytes being isolated with a micromanipulator.

In the attempts to produce drug resistance, known numbers of parasites were inoculated into 4 to 7 days-old chicks and treated with the drug in twice daily doses for 3 ½ days following inoculation. The doses of drug chosen were such that the growth of the parasites was inhibited but the infections were not completely eradicated. At the end of the course of treatment, the intensity of infection was determined by parasite counts. The infected blood from each treated chick was inoculated into a fresh host which was not treated with the drug and in which, therefore, the surviving parasites from the previous course of treatment multiplied. Using the birds in which an infection of suitable intensity developed most rapidly as donors, parasites, in similar number to those inoculated into the birds exposed to the previous course of drug treatment, were inoculated into groups of chicks which underwent a similar course of drug treatment. Thus the strain was subjected to courses of treatment with metachloridine alternating with the growth of the surviving parasites in untreated birds.

No enhancement of resistance was detected at the end of the first or second course of treatment, though infections in more than 500 chicks were studied; but in 13 out of 15 serial experiments an enhancement of resistance was first detected after 3 to 5 courses of treatment. Two pure lines of *P. gallinaceum* were used in the experiments, but no difference in the development of resistance could be observed in them. The rate of the development of resistance could not always be related to the size of the inoculum exposed to the action of the drug; but with the largest inocula (10^9 parasites) an enhancement of resistance was observed after the minimum number of courses of treatment (3), whereas with the smallest inocula (2.5×10^7 parasites) no enhancement of resistance could be detected after 7 courses of treatment. The size of the dose of drug, within the range tested, did not appear to affect the rate of the development of resistance. In some experiments resistance appeared to develop suddenly, in others more gradually.

For comparison with these experiments in which resistant infections developed from normal populations during drug treatment, some experiments were performed in which groups of chicks were inoculated with mixtures of known numbers of resistant and sensitive parasites. The resistant parasites were from a strain which had been made highly resistant to metachloridine. The number of resistant parasites in an inoculum varied from 1 to 10^6, but in each inoculum the number of sensitive parasites was 5×10^7. The birds thus inoculated were treated with a dose of metachloridine inhibitory to normal parasites (0.1 mg/20 mg). With inocula containing less than 10^6 resistant parasites no increase in parasite count was observed at the end of a single course of treatment, but when survivors were allowed to multiply in untreated birds and were then inoculated into birds which received drug treatment, heavy infections were produced in the treated birds if 10^3 resistant parasites had been present in the original inoculum. In several experiments the presence of a single resistant parasite, as assessed by dilution, in the original inoculum, was sufficient to produce a considerable increase in the parasite count after the second course of treatment.

The suddenness with which resistance appeared to develop in some of the strains undergoing serial courses of treatment, and the fact that the loss of sensitivity to the drug became apparent after the parasites had been multiplying in the absence of the drug, did not support the hypothesis that resistance was due to adaptation to the drug.

The stability shown by resistant parasites in the absence of the drug also did not favour this hypothesis. Thus, one strain, maintained in untreated birds from the time that an increase in parasite count could first be detected, had suffered no loss in resistance at the end of 43 days, or after mosquito transmission.

In the serial experiments, in view of the large numbers of chickens inoculated, if any resistant parasites had been present in the original inocula an increase in the parasite count should, by comparison with the experiments with mixed inocula, have been observed in some of the chicks at the end of the second course of treatment. No such increase was observed, however, before the end of the third course of treatment. If therefore resistance arises by spontaneous mutation independently of the drug it must be assumed that the mutants are present in the normal population with a frequency considerably lower than 1 in 5×10^7 parasites. The sudden increase in the parasite count might also be interpreted as resulting from a high rate of mutation occurring only after parasites had been exposed to the drug for a certain period.

With the exception of proguanil resistance as produced in *P. gallinaceum* by sulphadiazine (Bishop & McConnachie, 1948, 1950), metachloridine produces resistance in this parasite more rapidly than any other antimalarial compound tested. Other antimalarial compounds which produce resistant strains of *Plasmodium* relatively readily under laboratory conditions are proguanil, pyrimethamine, and two 2:4-diaminopteridines. Cross-resistance tests have shown these compounds to be related in their mode of action, which appears to be directed against the folic acid metabolic pathway. There is evidence from other sources that folic acid may play some part in the synthesis of nucleic acids, and it is of interest that the action of these compounds upon the malaria parasite has been shown, by several workers, to be directed against the dividing nucleus. Nothing, however, is known of the mode of action of metachloridine. A metachloridine-resistant strain showed no resistance to pamaquin, mepacrine, quinine, chloroquine, proguanil or sulphanilamide, and only slight resistance to sulphadiazine, sulphapyridine and sulphathiazole (Bishop & McConnachie, 1953). Moreover, its inhibitory action upon *P. gallinaceum* is not reversed by *p*-aminobenzoic acid (Brackett & Waletzky, 1946) or pteroylglutamic acid (Bishop & McConnachie, 1953), and it does not potentiate the antimalarial action of proguanil. However, although its mode of action appears to differ from that of other antimalarial compounds, the rapidity with which it produces resistant strains of *Plasmodium* suggests that it acts upon some metabolic pathway which can be replaced readily and efficiently.

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THE ESTABLISHMENT OF CENTERS FOR THE PRESERVATION OF STRAINS OF MALARIA PARASITES

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INTRODUCTION

For more than 30 years the knowledge and treatment of malaria have been greatly advanced by the maintenance and study of strains of malaria parasites in human patients undergoing therapy for neurosyphilis. These studies have been carried out at a number of places, with perhaps the most important being: (1) Rumania; (2) Epsom (Horton), England; (3) Tallahassee, Florida, and (4) Columbia, South Carolina, U. S. A. During recent years the number of neurosyphilitics presented for malaria therapy has decreased considerably, and the experimental malaria programs have been necessarily curtailed. This has posed a considerable problem in the maintenance of multiple malaria strains at the various centers of research.

This problem has been compounded by the current efforts toward world-wide malaria eradication. The success, or approaching success, of this program in various parts of the world makes it difficult, and eventually will make it well nigh impossible, to replace strains which may be lost because of a shortage of recipients requiring therapeutic malaria.

It is fortunate that the efforts of a number of investigators over the past 20 years have culminated in the development of practical methods for the preservation of viable malaria parasites for extended periods of time (Coggeshall, 1939; Manwell and Jeffery, 1942; Weinman and McAllister, 1947; Jeffery and Rendtorff, 1955; and others).

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Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 91-94, 1959

TECHNIQUES

Both the asexual forms of the malaria parasite in whole blood and the sporozoites may be successfully preserved by low-temperature freezing. Samples of freshly-drawn, citrated blood containing the parasites are placed in vials — usually about 5 cm^3 in a 10 cm^3 vial. The vials are immersed in a bath of solid CO_2 in 95 per cent ethyl alcohol and agitated until frozen. Mosquito salivary glands containing sporozoites are dissected using sterile techniques and the glands — usually about 10 per sample from a well infected lot of mosquitoes — suspended in 2 to 5 cm^3 of human serum or plasma. This suspension is placed in an appropriate vial (5 to 10 cm^3), immersed in the solid CO_2-alcohol mixture and agitated until frozen.

Vials of frozen material are transferred to storage boxes containing solid CO_2 or to mechanical freezers which maintain a temperature around — 70° C. While the critical temperature for loss of viability is not known with certainty, it is likely that this occurs prior to thawing temperatures, and for this reason the more reliable solid CO_2 storage may be preferable to the mechanical. A suitable low-temperature cabinet is available in England at a cost of about £ 500; it consists of 20 sheet aluminium inner containers each having 20,4″ × 3″ × 2″ deep compartmens and 5″ deep aluminium insulated lids fitted with locking handles; the whole is covered with a 6″ thickness of insulation, enclosed in a plastic coated sheet metal outer casing, and a counter balance arrangement is provided for the lids. Similar cabinets are produced in the U. S. A. and elsewhere.

When the frozen material is needed for use the vials are withdrawn from storage and thawed immediately prior to intravenous injection of the infective material. Thawing is generally done in a water bath between 37° and 40° C. Care must be taken not to overheat, but thawing should be rapid. Usually about 10 cm^3 of infected blood is used, when parasite density is reasonably high; if densities are very low, as much as 20 to 30 cm^3 should be used. Five to ten well infected salivary glands usually provide a good infective inoculum, but here again more can be used if infections are sparse or light.

Shipment of frozen material from place to place is successful if the material is maintained at low temperatures with solid CO_2. To date blood stages and sporozoites have been successfully preserved for periods of about four years, and there is no reason to believe that much longer periods would not be possible. However, it still seems desirable to replenish the preserved material at somewhat shorter intervals (one to two years) wherever practicable. Occasional failures are encountered and there is some evidence that the proportion of failures rises with extension of the time of preservation to three, four, and five years.

Special uses

Besides human malaria parasites, many species of animal plasmodia are employed in biological or chemotherapeutic research, and preservation of such strains deserves equal attention. Unlike the human parasites, the conservation of animal ones does not depend upon a supply of neurosyphilitics, but two other factors are important here: (1) continual blood passage of several important parasites leads to rapid disappearance of gametocytes and other fundamental changes in the strain [e. g., *Plasmodium knowlesi* (Hawking *et al.*, 1957), *P. gallinaceum* (Greenberg *et al.*, 1950, 1951), *P. cathemerium* (Gambrell, 1937)] — preservation of the original parasites would prevent these changes — and (2) maintenance of strains in animals like chimpanzees, monkeys or even canaries is expensive, and a considerable economy would be effected if «dry ice» were substituted for the animal.

Previous studies have shown the practicability of preservation of avian plasmodia by methods similar to those used with the human parasites; further studies on avian and saurian malaria may reveal techniques better suited to parasites living in nucleated erythrocytes. It is already known that blood parasites like trypanosomes survive better at low temperatures when glycerol is added to the medium (Polge and Soltys, 1957).

To preserve a species from extinction is one of the most important duties of a zoologist, and here we have an easy way of doing so, for a large group of animals — the blood parasites.

PROPOSAL

Because of (1) the reduction in numbers of neurosyphilitics available for induced malaria, (2) the elimination of malaria from various parts of the world, and (3) the relative ease of preservation of viable malaria parasites, the following is proposed for consideration and study:

1. Certain centers of research, probably those with facilities for induced malaria, be requested to preserve strains of human malaria parasites already in use experimentally and to acquire further representative strains from various parts of the world. These reference strains would then provide a basis for future studies on mosquito transmission, susceptibility to drugs (i. e., comparison with strains from the same areas which appear to have become resistant to drugs), etc.
2. These same centers or others might be expanded or established for the preservation of experimental strains of plasmodia of lower animals, of other human pathogens, as the trypanosomes, and of other protozoan parasites of man and lower animals.

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LA TRANSMISSION DE L'IMMUNITÉ ACQUISE ET DE LA RÉSISTANCE NATURELLE À *PL. BERGHEI* DES RATS À LA DESCENDANCE

N. A. Demina

L'étude de la transmission de l'immunité de la mère à la descendance est un problème des plus actuels de l'immunologie.

La transmission de l'immunité des mères immunes aux enfants est connue dans les cas des infections de l'étiologie différente, à savoir bacteriologiques virulentes, protozoaires et dans les cas de certaines helminthiases.

En ce qui concerne le paludisme, cette question n'a pas été mise à l'étude expérimentale avant la découverte de *P. berghei*. Toutefois les publications scientifiques comportent des indications constatant que dans le cas du paludisme humain dans les foyers hyperendémiques a lieu la transmission de l'immunité de la mère aux enfants.

Nous avons pu entreprendre l'étude expérimentale de ce problème après avoir reçu, grâce à l'amabilité du professeur Jaswant Singh, directeur de l'Institut du Paludisme d'Inde, une souche de *P. berghei*.

Il a été démontré par les recherches de Bruce-Chwatt (1954), Bruce-Chwatt et Gibson (1956), Terry (1955), Serguiev et Demina (1957) au cours des expériences réalisées sur les rats que la transmission de l'immunité des femelles immunes aux ratons a lieu et s'effectue par le lait. Les études ultérieures ont aussi permis d'établir (Demina, 1958) la transmission de l'immunité par le placenta. Dans le présent exposé nous rapportons quelques résultats des recherches déjà publiées et de celles à publier.

Pour révéler l'immunité chez les ratons nés des femelles immunes il importe avant tout que la quantité de parasites prélevés pour leur infection ne soit ni trop grande ni trop petite afin d'éviter «la rupture» de l'immunité ainsi que l'infection inapparente (dans le cas de l'absence de l'immunité).

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Les résultats les plus précis ont été obtenus lors de nos expériences dans le cas de l'infection intrapéritonéale des ratons — 1 000-10 000 parasites/20 g.

L'application de cette méthode a permis d'établir le mécanisme de la transmission de l'immunité des rats immunes aux ratons (la transmission par le lait et le placenta) ainsi que la durée de la manifestation de l'immunité. Elle a permis également de mettre au point une série d'autres questions.

Au cours d'une expérience nous avons observé se manifester l'immunité chez un raton à partir de l'âge de 24 heures. Dans cette série d'expériences nous avons analysé le sang de 58 ratons nouveau-nés produits par les rates immunes. On a révélé des parasites chez un raton né d'une femelle immune ayant subi une infection réitérative (20 000 parasites sur 20 g) deux jours avant les couches. Au bout de 2 jours après cette infection elle a produit 9 ratons. Il a été procéder à l'analyse de leur sang à l'âge de 24 heures. On a constaté chez un raton (N 7) une grande quantité de parasites (jusqu'à 25 parasites dans le champ visuel). Les analyses du sang opérées par la suite ont révélé que le raton avait vaincu très vite l'infection, ce qui atteste la présence chez lui de l'immunité à *P. berghei.* Au bout d'un jour le nombre de parasites restant aussi grand que la veille on a constaté une petite quantité de formes morphologiquentement changées des parasites en phase de «crise». Encore un jour plus tard la quantité de parasites a sensiblement diminué dans le sang et tous ils sont représentés par les formes en phase de «crise». En même temps on a noté une quantité plus importante de normoblastes que chez les ratons normaux du même âge. Par la suite le raton a manifesté la parasitémie instable, et puis il guérit. L'infection aurait été mortelle à cet âge s'il s'agissait d'un raton né d'une femelle n'ayant pas subi d'infection.»

Nous supposons que le raton N-7 a été infecté lors de notre expérience dans la période embryonnaire. De quoi partons-nous en avançant cette supposition? L'infection de la femelle a été effectuée intrapéritonéalement duex jours avant les couches. Cependant l'utérus très grand a empêché d'exécuter cette manipulation. Au moment de l'injection on avait l'impression que le sang était introduit de la seringue sous une certaine pression. Et voilà pourquoi nous en sommes venus à la supposition que le sang fût introduit non pas dans la cavité abdominale mais plutôt dans l'utérus. Les résultats obtenus par l'analyse du sang du raton N-7 ont confirmé la justesse de notre supposition.

Par quels facteurs est déterminée la transmission de l'immunité des rates aux ratons?

Dans le cas de la transmission de l'immunité par l'intermédiaire du placenta ce n'est pas une immunité active résultant d'une infection congénitale. Et tout pareillement au cas du paludisme humain l'infection congénitale chez les rongeurs n'a lieu qu'à condition de la lésion du placenta (Werner, 1956 et 1956-*a*; Kunert et Werner, 1957).

Nous avons fait des expériences sur les ratons en leur introduisant du sérum des rates immunisés. Et ces expériences ont montré que ces sérums n'ont pas de propriétés curatives et prophylactiques (sous presse). Ceci est également connu pour la tierce benigne, pour certaines formes du paludisme des oiseaux (sauf l'infection provoquée par *P. circum flexum* — Manwell et Goldstein, 1938, 1940) et pour le paludisme des singes (à l'exception de l'infection provoquée par *P. knowlesi* — Coggeshall et Kumm, 1937, 1938; Coggeshall et Eaton, 1938).

De ce fait il n'est pas clair de quelle manière se produit l'immunisation des ratons par le lait. Il est connu que dans le lait il y a le plus souvent moins d'anticorps que dans le sérum des mères immunes. Donc la question relative à la transmission de l'immunité des rates immunes aux ratons n'est pas résolue à l'heure actuelle et nécessite une étude supplémentaire.

Quand nous mettons au point la question concernant la transmission de l'immunité à *P. berghei* des rates immunisées à la descendance, nous nous heurtons à quelques phénomènes qui rendent cette étude plus compliquée. À de tels phénomènes se rapportent l'existence de la résistance naturelle temporaire à *P. berghei* chez certains animaux, la différente durée de l'infection chez de différents animaux, les fluctuations individuelles de l'intensité de l'immunité chez certains individus, ainsi que fort probablement une différente intensité de l'immunité aux différentes phases de la période métacritique de l'infection.

Dans le cas du paludisme de rongeurs l'immunité a, comme on le sait, quelques particularités en comparaison avec d'autres formes de l'infection du paludisme. La durée de l'infection chez les rats connaît des fluctuations sensibles à partir de 1-1,5 mois jusqu'à 2 ans et plus (Raffaele et Baldi, 1950; Carradetti, 1950; Carredetti et Verolini, 1957;

Black, 1951; Rama Krishnan, Satyá Prakash et Krishnaswami, 1951; Vincke, Peters et Franki, 1953; Draper, 1954).

À l'infection du *P. berghei* la période métacritique se caractérise par un état de la prémunition à laquelle succède la phase de l'immunité stérile. Par la suite les animaux perdent l'immunité et redeviennent réceptifs.

Il est connu que dans le cas du paludisme le rôle immunisant revient aux parasites erythrocitaires. Avec leur disparition du sang périphérique l'irritation d'antigène cesse et peu à peu l'immunité s'éteint.

Par analogie avec les infections provoquées par d'autres espèces de parasites paludéens il est possible de supposer que dans le cas du paludisme de rongeurs l'immunité chez les rats a été plus active à la période de la présence des parasites erythrocitaires dans le sang qu'à la phase de l'immunité stérile, surtout à des étapes avancées. Par la suite, la transmission de l'immunité des femelles immunes à la descendance survenant à de différentes étapes du processus d'infection serait garantie inégalement. Elle serait plus effective à la période de prémunition, c'est-à-dire à la présence de l'irritation d'antigène.

Aux premiers stades de la phase de l'immunité stérile, tant que se produit l'action d'antigène des parasites erythrocitaires la transmission de l'immunité des rates immunes aux ratons doit avoir lieu. À une période plus avancée de cette phase, la phase alors que l'immunité s'éteint peu à peu, sa transmission à la descendance n'a pas lieu ou si elle se produit l'immunité est très faible chez les ratons, ce qui ne les préserve pas de l'infection.

Donc à cette phase d'infection l'intensité de l'immunité chez les femelles peut se manifester suffisant pour résister à l'infection réitérative, mais insuffisante pour qu'elle soit transférée aux ratons. Une telle possibilité a été signalée par nous (Demina, 1958) dans nos recherches. À l'heure actuelle nous mettons cette question à l'étude expérimentale.

Il est difficile de dire en quelle mesure ceci serait régulier, cependant nous disposons des données qui montrent que lorsque les parasites sont absents dans le sang des femelles immunes l'immunité est prononcée à un degré très faible chez les ratons. Pour tirer la conclusion définitive d'autres expériences sont nécessaires.

Avec la disparition totale de l'immunité les femelles redeviennent réceptives. Nos expériences ont montré que dans ce cas les ratons sont également réceptifs.

Le phénomène de la résistance naturelle temporaire à *P. berghei* qui s'est manifestée chez des rats blancs et des souris blanches présente un grand intérêt. Il est connu que se phénomène se manifeste plus souvent dans le cas de l'infection sous-cutanée que dans celui de l'infection intrapéritonéale. Cette résistance temporaire est une résistance dynamique et non pas statique, car elle est conditionnée non pas par les propriétés constitutionnelles stables particulières à cette catégorie d'animaux, mais par un complexe des propriétés physiologiques susceptibles de changer avec le temps. Comme il est connu, ces animaux tombent malades en règle générale par la suite d'une des infections ultérieures.

Cette résistance temporaire n'est pas déterminée par la déficience dans l'organisme de l'hôte de telles ou telles substances nécessaires pour le développement et la reproduction des parasites (par exemple, dans le cas où les animaux sont mis à la diète lactée). C'est que dans ce cas la résistance se manifesterait indépendamment de la méthode d'infection. Donc, les parasites sont soumis à des actions nocives dans le tissu souscutané où a été opérée l'inoculation ou pendant leur migration du lieu d'inoculation au système circulaire.

Toutefois, une pénétration rapide dans le sang (dans le cas de l'infection intrapéritonéale, comme on sait, au bout d'une ou de quelques minutes — Schneider et Schneider, 1950; Fabiani et d'autres, 1951; Black, 1952) ne signifie pas que se trouvent ainsi garanties les conditions favorables au dévéloppement et à la reproduction, car dans le cas de cette infection chez une partie d'animaux l'infection ne se développe pas.

La différente intensité d'infection chez de différents animaux montre que les conditions pour la reproduction des parasites ne sont pas les mêmes dans les différents organismes de différents individus. Les formes données par Sergent et Poncet (1955) présentent de l'intérêt. Dans leurs expériences des résultats négatifs se sont manifestés dans le cas de l'infection sous-cutanée presque avec le même pourcentage que la faible infection dans le cas de l'infection intrapéritonéale (respectivement 12 et 14 pour cent). Ces données montrent que parmi les rats dont disposent l'auteur pour ses expériences il y avait une catégorie d'animaux résistants. Dans le cas de l'infection intrapéritonéale cette résistance a été vaincue. Pourtant les parasites ayant pénétré dans le sang de telles rats se sont trouvés dans des conditions défavorables pour leur développement, ce qui a amené l'infection faible chez elles.

Nous avons montré que la réceptivité des ratons produite par les femelles normales correspond à celle de leurs mères. La plupart de ratons nés des femelles résistantes ont été également résistants. Ce fait a été confirmé par nos autres expériences où nous inoculions les ratons faisant partie de différentes portées, reçus d'une pépinière. Nous supposions que dans ces groupes de ratons produits par de différentes femelles il y eût des individus réceptifs et résistants à *P. berghei*. Et en effect, outre des ratons réceptifs, il y avait des ratons qui ont résisté dans quelques cas à l'infection aussi massive que 500 000-1 000 000 parasites sur 20 g de poids, introduits intrapéritonéalement.

Nous avons fait le calcul de l'intensité de l'immunité chez les femelles immunes, de celle de leurs ratons (de 2-2,5 semaines), et de celle des ratons de 3-4 semaines ayant une résistance naturelle produite par les femelles n'ayant pas subi d'infection.

Ces calculs ont été faits comme suit: suivant nos observation les femelles immunes sont capables de résistir à une infection massive jusqu'à 500 000 000 parasites-50 000 000 parasites sur 20 mg de poids, et ceci n'est pas du dernier limite. Fabiani et Wargues (1951), qui injectaient aux rats 500 000 000, 800 000 000 de parasites, et Krishnaswami, Satya Prakash et Ramankrishnan (1953), en injectant 2 000 000 000 de parasites, n'ont pas reçu une phase aiguë d'infection.

Les ratons produits par les femelles immunes subissent bien (sans en être affectés) 1 000-10 000 parasites et, suivant les données de Bruce-Chwatt et Gibson (1957), 50 000 parasites. Quelques ratons normaux comme nous l'avons indiqué ci-haut peuvent résister à l'infection de 500 000, 1 000 000 parasites.

Si nous prenons 10 000 parasites pour la quantité initiale et le marquerons comme unité nous pourrons dire que l'intensité de l'immunité chez la femelle ayant vaincu l'infection correspond à 5000-50 000 unités et plus. Ainsi se manifeste la plus grande intensité de l'immunité chez les femelles ayant vaincu l'infection. Et c'est un fait remarquable, que chez certains ratons normaux la résistance non-spécifique est de 50-100 fois plus grande que celle de l'immunité spécifique chez des ratons nés des femelles immunisées.

A STUDY OF RELAPSE *PLASMODIUM BERGHEI* ISOLATED FROM WHITE MICE

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INTRODUCTION

It has been previously demonstrated that *Plasmodium berghei* infections of white mice could be converted into a latent state with Atabrine treatment. It was also observed that latent infections of mice relapsed with considerable frequency in spite of the fact that the mice were resistant to reinfection (Cox, 1957, 1958). On the other hand, the proneness of rats to relapse following splenectomy (Galliard and Lapierre, 1950; Black, 1951) and the susceptibility of splenectomized voles to reinfection (Zuckerman, 1953) indicate that a loss of acquired immunity might be a factor in the relapse of *P. berghei*. It therefore seemed desirable to further investigate the relapse phenomenon to determine if factors in addition to loss of immunity might be involved.

The present paper is a report on experiments in which the resistance of latently infected mice to reinfection with *P. berghei* taken from mice with relapsed infections was compared to the resistance to reinfection with stock *P. berghei* that has been maintained in normal mice.

MATERIALS AND METHODS

The source maintenance and standardization of the stock *P. berghei* have been previously described (Cox, 1957).

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[1] Also published as a study of relapse *Plasmodium berghei* infections isolated from white mice, *Jour. Immunol.*, 82: 209-214, 1959.

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 101-106, 1959

In the experiments Atabrine treatment consisted of daily intraperitoneal injections of 0.5 mg of aqueous Atabrine per mouse for 5 days.

The 3 relapse *P. berghei* infections used were taken from 3 different mice; each of which had a relapse 90 or more days after infection. Two drops of blood from the tail of a mouse with relapse was suspended in 1.0 ml of saline. This suspension was then injected intraperitoneally in 0.2 ml amounts into normal mice. In the first and second experiment, the mice used for isolating the relapse infection were the sources of the relapse infections. In the third, the relapse infection was maintained in normal mice by serial passage until it was used.

White Swiss albino mice 8-12 weeks old taken from the departmental colony were used in all experiments.

The data from the experiments expressed as % mortality was subjected to statistical analysis using «the standard error of the difference between the two proportions» (Hill, 1949).

EXPERIMENTAL DESIGN

In these experiments mice were treated with Atabrine 8 to 12 days after infection with *P. berghei*. 5 to 7 days after treatment the mice were randomly distributed into 3 approximately equal groups of mice. The mice of Group I were challenged with a relapse infection and the mice of Group II with the stock infection. The mice of Group III, which served as latent infection controls, were not challenged.

In the first and second experiment control groups of normal and treated normal mice were also given the challenging infections. In the third, 2 groups of 5 mice were included, 1 group for each challenging infection, as infectivity controls.

RESULTS

In the first experiment 33 mice were distributed into 3 groups 7 days after treatment and the challenging infections, standardize so that each mouse received 50,000 parasitized RBC were administered. The challenging infections were also given each to a group of 11 normal and to a group of 11 treated normal mice. The number of deaths in

Groups I, II and III, 30 days after challenging infection is shown in Table I. The survivors had all developed latent infections at that time and had the appearance of normal mice. The mice of the normal and treated normal control groups died within 27 days after infection.

In the second experiment 66 mice were infected and treated. Five days after treatment the surviving 61 mice were distributed into groups of 21, 20 and 20 mice. The challenging infections standardized at 750,000 parasitized RBC were given. Again groups of normal mice (21 per group) and groups of treated normal mice (11 per group) were included as controls for the challenging infections. The number of deaths 30 days after challenge in groups I, II and III are shown in Table I. Again the survivors all developed latent infections and the mice of the control groups all died within 27 days after infection.

TABLE 1 — *The number of mice used, the number of deaths and the percent of deaths in groups of mice with induced latent* Plasmodium berghei *30 days after challenge with relapse* P. berghei *(group I), challenge with stock* P. berghei *(group II) and in unchallenged latent infection controls (group III) in 3 experiments and the totals for the groups of the 3 experiments*

Expt.	Group I challenged with relapse infection			Group II challenged with stock infection			Group III latent infection control		
	No. mice used	No. mice used	% mice dead	No. mice dead	No. mice dead	% mice dead	No. mice dead	No. mice dead	% mice used
1	11	6	54.5	11	3	27.3	11	1	9.1
2	21	15	71.4	20	6	30.0	20	7	35.0
3	28	21	75.0	28	12	42.8	28	9	32.1
Totals of the 3 experiments	60	42	70.0	59	21	35.6	59	17	28.8

In the third experiment 90 mice were infected and treated. Seven days after treatment the 84 survivors were distributed into 3 groups of 28 mice and the challenging infections, standardized at 1,000,000 parasitized RBC per mouse were given. Treated and untreated normal controls groups were not used. However, two groups of 5 normal mice, one for each challenging infection were used as viability controls. The number of deaths in groups I, II and III, 30 days ofter challenge is shown in Table 1. The survivors again appeared healthy by the thritieth day and the two groups of infection control mice all died within 25 days after infection.

The results of the statistical analysis of the mortality data for groups I, II and III for the 3 experiments is shown in Table 2.

TABLE 2 — *Statistical analysis*[1] *of the data*

Expt.	Groups compared	Total % mortality in groups compared	Standard error of the groups compared	Difference in % mortality between groups	No. standard errors	Probability
1	I & III	31.8	19.9	45.4	2.37	0.0214
	II & III	18.3	16.4	18.2	1.12	0.23 NS[2]
	I & II	40.8	20.9	27.2	1.30	0.19 NS
2	I & III	53.7	15.5	36.4	2.36	0.0214
	II & III	32.5	14.8	5.0	0.34	0.50 NS
	I & II	51.2	15.6	41.4	2.66	0.0093
3	I & III	53.7	13.3	42.9	3.10	0.0019
	II & III	37.5	12.5	10.7	0.88	0.36 NS
	I & II	59.0	13.1	33.2	2.50	0.0124
Totals of the 3 expts.	I & III	49.6	9.1	41.2	4.55	0.00006
	II & III	32.2	8.6	6.8	0.79	0.424 NS
	I & II	52.8	9.19	34.4	3.75	0.00022

[1] The standard error of the difference between the two proportions.

[2] Probability greater than 0.05 considered not to be a significant difference.

DISCUSSION

Mice with induced latent *P. berghei* infections were subjected to challenging infections of *P. berghei* isolated from mice with relapsed infections, and to challenge with the stock *P. berghei* that has been maintained by blood transfer in normal mice. In each of the 3 experiments there was a greater mortality among mice challenged with relapse infection than among mice challenged with the stock *P. berghei*, or among unchallenged latent infection control mice. In the 3 experiments a total of 60 mice challenged with relapse infections had a 70 % mortality; while 59 mice challenged with stock *P. berghei* had 35.6 %, and the 59 unchallenged latent infection control mice had 28.8 % mortality.

Statistical analysis of the mortality data indicated a significant difference between the mortality of mice challenged with relapse infections and the mortality of mice challenged with stock *P. berghei*. It was also indicated that differences in mortality of mice challenged with stock infection and the mice of the latent infection control groups was not significant.

The data obtained from groups of normal mice and groups of treated normal mice that were given the challenging infections showed that the relapse infections were no more lethal for normal mice than was the stock *P. berghei*, and also that the Atabrine treatments had not influenced the mortality data. It was therefore indicated that an increase in the virulence of the parasite was not responsible for relapsed infections.

From the results of these experiments it is suggested that relapses of latent *P. berghei* infections of white mice result from biological variation in an immune host. From such variation, variants develop that are capable of thriving in the immune host to the extent that parasitic recrudescence or relapse occurs. Further, it is suggested that these variants also thrive when they are transfered to mice immunized by the stock infection and produce a greater mortality than does a challenge with an equal inoculum of the stock infection.

SUMMARY

In each of 3 experiments mice with latent *P. berghei* were shown to be more susceptible to reinfection with parasites isolated from a relapsed *P. berghei* infection than they were to the stock infection that has been maintained in normal mice. On the other hand it was shown that the relapse infections were no more lethal for normal mice than was the stock infection.

It is suggested that relapses of latent *P. berghei* infections of mice result from biological variation in an immune host in which variant parasites capable

of thriving in an immune host are produced. It is also suggested that these variants also thrive when transfered to new mice that have been immunized with stock infection and cause a greater mortality than does a challenge with the stock infection.

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MASS SUPPRESSION OF HYPERENDEMIC VIVAX MALARIA WITH HYDROXYCHLOROQUINE

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INTRODUCTION

The objective of this study was to evaluate the therapeutic and suppressive effects of hydroxychloroquine (Plaquenil[1]) against hyperendemic malaria under field conditions. The study was made in a small village east of the city of Beirut, Lebanon, during the period from April, 1953 to June, 1954.

Hydroxychloroquine is 7-Chloro-4-(4'-(N-ethyl-N-β-hydroxyethylamino)-1'-methylbutylamino)-quinoline. It is a 4-aminoquinoline which differs from chloroquine in that an hydroxyethyl group is substituted for one of the ethyl groups on the tertiary aminonitrogen. It was first synthesized and described by Surrey and Hammer (1). In terms of base, 500 mg of diphosphate salt is essentially equivalent to 400 mg of the sulfate salt.

The antimalarial activity of hydroxychloroquine against *Plasmodium lophurae* infection in ducks and *P. cynomolgi* infection in rhesus monkeys is about the same order as that of chloroquine [Dennis *et al.* (2)]. Replacement of a terminal hydrogen by a hydroxy group reduced the toxicity of chloroquine without causing a significant loss of antimalarial activity. The acute oral toxicity of hydroxychloroquine for Swiss mice and for dogs was reduced to one-fifth and acute i. v. and i. m. toxicity for Swiss mice was reduced to one-third that of chloroquine. Its subacute oral toxicity for rats in a 21-day test was approximately half that of chloroquine, and dogs tolerated daily doses as high as 20 mg base per kg for a period of 15 weeks. Monkeys showed excellent tolerance to daily doses of 60 mg base per kg for 10 months (3).

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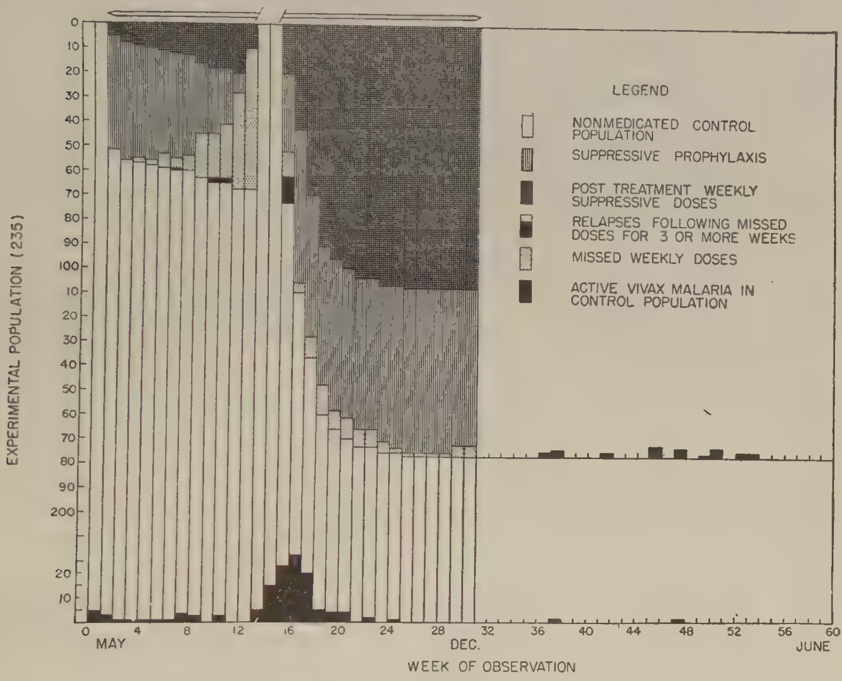
[1] Plaquenil diphosphate was provided by the Sterling-Winthrop Research Institute for the Winthrop Laboratories Inc.

In the Island of Haiti, Loughlin *et al.* (4) treated 75 cases of falciparum malaria with hydroxychloroquine diphosphate. They used single 1 to 2 gm doses, according to age, and commented on its rapid effect on parasitemia and fever, as well as on its low toxicity. In Honduras, Central America, Hoekenga (5, 6, 7) (1953-1955) treated 213 cases of acute malaria with hydroxychloroquine diphosphate. Twenty-five patients received a single oral dose of 0.75 gm and 125 received 1.25 gm. Except with the lower oral dose, both the immediate and late results were quite good, and compared favorably with the other 4-aminoquinolines in common use. He also treated 26 acute falciparum infections with intravenous doses of 0.36 gm in 500 cm^3 of normal saline, and in 37 others the same dose dissolved in 9.0 cm^3 of saline was injected intramuscularly with excellent results. Toxic side effects were not noted on any of the regimens used. In a Panamanian village with a high rate of malarial infection, Clark (8) (1954) used tablets containing 300 mg hydroxychloroquine base and 30 mg primaquine base for suppression of malaria. For 20 to 26 weeks he gave a single tablet once a week to adults; a half tablet once a week to children weighing 90 pounds or more; and a quarter tablet to children weighing less than 90 pounds. He treated ninety-three individuals of whom forty-nine (52.2 %) were positive at the beginning. After the first 3 weeks of suppressive medication only 6 subjects were found positive for malaria parasites on weekly examination of thick blood films. No toxic effects were noted in either children or adults.

LOCALE OF OUR FIELD STUDIES

Our field studies with hydroxychloroquine were carried out in Sed el Boshrié, a small semi-urban community of approximately 500 population, located about 7 km east of the city of Beirut, and in the valley of Ain Sheikh River where *Anopheles superpictus* breed profusely. The river is the main source of anopheline mosquitoes in the district, although many wells and cisterns used for water storage breed *Anopheles claviger*, which is also an effective vector of malaria.

Most of the adult population in the district worked in nearby factories. Mosquito nets were not used and houses were not screened. During the late summer of 1952 many of the inhabitants of Sed el Boshrié suffered from acute malaria. The following spring, in April of 1953, a spot survey of 162 persons gave the following information.



Of forty children below five years of age, eight (20 %) had enlarged spleens; and of forty-four children between five and twelve years old, 26 (61 %) had enlarged spleens. The Splenic Index of children twelve years and under, therefore, was 40. Of the seventy-eight individuals over twelve years of age thirty-one (40 %) had enlarged spleens. Immediately preceding our study a WHO malaria team had found a parasite index of 11 %. Relapses of vivax malaria appeared in the district as early as April 15, 1953 and between then and May 7, 1953 there were 14 cases of *Plasmodium vivax* infection. There were no physicians in permanent residence in the vicinity of Sed el Boshrié.

At the onset of our study the villagers were using quinine, quinacrine or chloroquine indiscriminately, irregularly, and in inadequate dosage.

PROGRAM

After a preliminary survey and consultation with the Director of Health of Lebanon, we adopted the following program to evaluate the suppressive and therapeutic properties of hydroxychloroquine as an antimalarial drug under field conditions.

1. The Department of Health agreed not to undertake mosquito control work in the area, leaving the anophelines free to infect the subjects without interference for the duration of the study.
2. We examined all individuals requesting suppressive or curative treatment. The examination included a brief history pertinent to bouts of fever within the previous year, and a record of the measurements of spleen and liver. The object was to observe the effect of hydroxychloroquine on these organs. Thick blood films were taken and examined from all cases of fever, from all persons with palpable spleen and liver and from all persons giving a history of an attack of fever during the current malaria season. We repeated thick-film examinations of all medicated subjects at intervals, and in every instance of malaise or fever.
3. We treated all cases of overt malaria with hydroxychloroquine followed by weekly suppressive medication for a period extending at least two months beyond the transmission season.
4. For prophylaxis we administered to a part of the population not suffering from patent malaria one dose of hydroxychloroquine weekly for the same period.
5. We observed the rest of the «non malarial» villagers as voluntary nonmedicated controls, and watched for cases of malaria developing among them. We gave to each new patent case a therapeutic course and subsequently included the patient in the group of similar cases receiving weekly suppressive medication.
6. We discontinued weekly suppressive medication at the end of December 1953 and instituted a full program of anti-mosquito control work with DDT in the entire area prior to the onset of the following

transmission season. We then placed the population under constant observation for:

a) Relapses of malaria in those who had been treated as active cases, and

b) For the appearance of overt malaria in subjects who had received no medication or only the suppressive regimen of hydroxychloroquine.

Three hundred and nineteen of the 500 inhabitants of Sed el Boshrié volunteered to participate in the study. Of the 319 participants, 74 were lost for various reasons; 10 were observed for only part of the study; and the remaining 235 were observed for the entire period.

DOSAGE SCHEDULE OF HYDROXYCHLOROQUINE USED FOR THE TREATMENT AND SUPPRESSION OF MALARIA

We used 0.25 gm tablets of hydroxychloroquine diphosphate. Each tablet contained 0.15 gm of hydroxychloroquine base.

Therapeutic dosage: For children under 5 years of age we gave a total of 1½ tablets. One tablet was given immediately and ½ tablet the next morning. For children over 5 and under 12 years of age, we gave 3 tablets; 2 tablets immediately and 1 tablet, the next morning. For children over 12 years of age and for adults, we gave a total of 6 tablets; 4 tablets immediately and 2 tablets, the next morning. All treated cases subsequently received weekly suppressive medication beginning one week after therapy.

Suppressive (prophylactic) dosage: For children less than 6 years of age, we gave ½ tablet; for children 6 to 12 years of age, we gave 1 tablet; and for older children and adults, we gave 2 tablets. Suppressive medication was given once a week as a single dose.

A detailed history of each volunteer was kept and is summarized chronologically in chart I and table 1. The recorded data show the following:

(1) The number of persons with symptomatic malaria presented for treatment each week,

Table 1 — *Weekly History of Experimental Population* (319)

Date of observation		Hydroxychloroquine medication			Number remaining as controls	Number of cases of malaria		Remarks concerning relapses
		Attacks * treated	Suppressive given	Doses missed		In controls	In suppressive group	
(1953)								
May	5	5	0	0	230	5	0	
	12	3	52	0	180	3	0	
	19	1	56	0	178	1	0	
	26	1	55	2	177	1	0	
June	2	1	56	2	176	1	0	
	9	1	53	6	175	1	0	
	16	1	55	4	175	0	1	28 day after interruption of suppressive medication.
	24	3	54	6	172	3	0	
July	1	2	45	18	170	2	0	
	8	2	45	18	170	0	2	17 and 26 days after interruption of suppressive medication.
	16	4	41	22	168	2	2	
	24	0	29	39	168	0	0	
August	1	0	10	57	168	0	0	
	24	33	52	11	139	23	10	26 to 59 days after interruption of suppressive medication.
September	1	27	106	4	98	27	0	
	8	21	129	8	77	21	0	
	16	5	149	11	70	5	0	
	24	4	159	7	65	4	0	
October	1	4	162	8	61	4	0	
	8	0	167	7	59	0	0	
	16	2	167	7	59	2	0	
	24	0	172	4	59	0	0	
Nevember	1	1	174	2	58	1	0	
	8	0	176	1	58	0	0	
	16	0	176	1	58	0	0	
	24	0	176	1	58	0	0	
December	1	0	176	1	58	0	0	
		0	173	4	58	0	0	
	16	0	173	4	58	0	0	
Jan.-June 1954 follow-up		25	0	—	—	2 (Primo)	23 (Relapses)	23 of 25 had history of malaria prior to start of study.

(2) The number of persons receiving suppressive doses of hydroxychloroquine each week,

(3) The number who had started suppressive medication but failed to take their medication,

(4) The number of nonmedicated subjects remaning as controls, and

(5) The number of relapses during the post-medication observation period.

The new cases of malaria appearing in the control group each week are shown initially in the «treatment» column at the time of first medication, and thereafter in the «suppression» column unless a subject failed to appear for the weekly dose.

OBSERVATIONS

On April 20, 1953 we examined and questioned the subjects and succeeded in observing 235 of the original 319 for the entire duration of the study. The group, ranging in age from 6 months to 75 years, included persons who were ill at the time of examination, those who had been ill recently, those with past history of malaria, with or without enlarged spleens, and healthy individuals who volunteered for examination and suppressive medication. We administered no treatment on the initial visit. Three weeks later, at the time of our second visit, 5 malarial patients were treated but no suppressive medication was issued.

At the time of our third visit the following week, 47 selected afebrile persons were started on suppressive medication. The 5 patients treated the previous week were free of symptoms and were added to the «suppression» group. Three new cases of malaria were seen and treated.

Since the transmission season had not started, active cases of malaria observed prior to May 26, approximately five weeks after the initial examination, were either relapses or instances of prolonged latency from the previous season. The first «primo» infection was observed on May 26 in a 3-year old boy who had no prior history of malaria and whose spleen had not been palpable when examined on April 20th.

TABLE 2 — *Analysis of thirty-three cases of vivax malaria observed August 24, 1953, after break in medication schedule*

Case No.	Original group	Sex and age (years)	Past history of malaria	Blood smear (Aug. 24)	Duration (weeks) [1]	Remarks
82	C	F 10 mo.	—	+		Primoinfection
83	C	F 22	—	+		»
141	C	F 14	—	+		»
144	C	F 15	—	+		»
145	C	F 47	—	+		»
146	C	M 45	—	+		»
148	C	F 14	—	+		»
183	C	F 8	—	+		»
194	C	F 5	—	+		»
195	C	F 25	—	+		»
239	C	F 2	—	+		»
296	C	F 2	—	+		»
299	C	M 10	—	+		»
184	C	F 2	—	—		Primoinfection, clinical malaria [2]
186	C	F 10	—	—		» » »
187	C	F 45	—	—		» » »
17	C	M 30	+	+		Superinfection or relapse
160	C	M 30	+	+		» » »
198	C	M 35	+	+		» » »
208	C	M 15	+	+		» » »
222	C	F 14	+	+		» » »
232	C	M 26	+	+		» » »
293	C	M 10	+	+		» » »
215	S	M 4-½	+	+	12	Last suppr. dose, 26 da. prior to fever
252	S	F 3	+	—	10	» » » 33 » » » »
260	S	F 13	+	+	8	» » » 59 » » » »
289	S	M 11-½	+	+	10	» » » 39 » » » »
290	S	M 14	+	+	9	» » » 47 » » » »
81	TS	M 2-½	+	+	11	Last suppr. dose, 35 da. prior to fever
108	TS	M 32	+	+	7	» » » 54 » » » »
262	TS	M 4	+	+	12	» » » 55 » » » »
263	TS	F 5	—	—	2	» » » 31 » » » »
295	TS	M 20	+	+	8	» » » 47 » » » »

C = Control group — no suppression or treatment.
S = Suppressive medication with hydroxychloroquine only.
TS = Treatment with hydroxychloroquine diphosphate followed by weekly suppressive medication with hydroxychloroquine.
[1] = Duration in weeks between first and last dose of suppressive medication.
[2] = Quinine self-administered for several days before blood was taken for smears.

During June and July, 5 individuals who interrupted their course of suppressive medication came down with acute vivax malaria 3 to 4 weeks after their last suppressive dose. All had a history of malaria during the previous season and had enlarged spleens.

During July and August there was an increasing reluctance on the part of the villagers to call for medication at the appointed time. It became necessary, therefore, to make a procedural change. We decided to visit the subjects in their homes in the evening. We took blood smears from all febrile individuals and we supervised the swallowing of the tablets. We resurveyed the village on August 16 but gave no medication until our next visit on August 24th. On this date we treated 33 persons for overt malaria which are analysed in table 2. Twenty-three were among 168 controls who had not received medication; the remaining 10 had been irregular in taking suppressive doses and came down with malaria from 26 to 59 days after their last suppressive medication.

The malaria transmission season terminated in October, but weekly medication was continued until December 16th. From November 8th until December 16th the village was visited 2 or 3 times a week searching for evidence of active malaria.

A week after terminating suppressive medication, we took thin and thick blood films from all persons who had been under suppressive medication. They were all negative for plasmodia. All houses in Sed el Boshrié were then sprayed with 5 % DDT, and again in April 1954. Throughout this six month period the population of the area was checked for relapses of malaria by house-to-house visits at 3-day intervals. Thick blood films were made routinely from all persons who complained of malaise, fever, diarrhoea or other illnesses regardless of the apparent nature of the disease.

SUMMARY OF RESULTS OF OUR FIELD STUDIES WITH HYDROXYCHLOROQUINE

1. *Summary of experience during the transmission season.*

a) *Therapeutic efficacy of hydroxychloroquine:* One hundred and forty-six attacks of vivax malaria in 137 individuals were treated with hydroxychloroquine diphosphate. Highly satisfactory results were obtained when two-thirds of the total dose was given immediately and one-third, the following day (i. e., a total of 1.5 gm for adults, 0.75 gm for children 6-12 years, and 0.375 gm for children under 6 years). Although the majority of febrile children receiving a suppressive dose of only ½ tablet (0.125 gm) were rendered afebrile, in a few instances this dosage was not adequate. There was, however, prompt clinical response when a whole tablet was given, followed by a half-tablet the next day. Data on the therapeutic regimens are summarized in table 3.

Table 3 — *Treatment of vivax malaria with hydroxychloroquine diphosphate*

	Age distribution		
	1-5 yrs.	6-12 yrs.	13 yrs. and over
Patients treated (137)	25	26	86
Therapeutic dose	0.375 gm	0.75 gm	1.5 gm
Control of symptoms	Good	Good	Good
Post-tr. suppression (127)	21	22	84
Suppressive dose	0.125 gm	0.25 gm	0.5 gm
Av. no. of weeks	17.4	16	16
Av. total drug intake	2.175 gm	4.0 gm	8.0 gm
Relapsed (6 mo. follow-up) [1] (18/112) (16 %)	5/19	0/22	13/71
Days after last dose	60-178	—	60-180

[1] Total attacks treated, including relapses = 146.

b) *Suppressive efficacy of hydroxychloroquine:* Twenty-three subjects who had no history of prior malaria and who regularly received weekly suppressive medication did not contract malaria. In contrast, 64 of the 76 controls, (or 87 %), not receiving prophylactic medication, developed overt malaria.

During the same period, 34 subjects who had previously had malaria and who regularly took weekly suppressive medication, did not contract malaria. Eight others, failing to take the drug regularly, developed the disease. In contrast, 46 of the 78 (or 59 %) nonmedicated controls developed malaria.

In other words, no attacks of malaria occurred among 57 persons who regularly received hydroxychloroquine. However, 118 cases developed among 162 nonmedicated controls or persons whose prophylactic medication was irregular, representing an attack rate of 72.8 %. Sixty-four of these 118 cases were «primo» attacks. The results of the suppressive regimen are presented in table 4.

2. Observation for relapses during the post-transmission season after cessation of suppressive medication.

During the six-month period of post-medication observation, 25 authenticated attacks of *P. vivax* infection occurred. Eighteen relapses occurred among the 103 confirmed cases of vivax malaria treated with hydroxychloroquine; their symptoms appeared 60-180 days after discontinuing suppressive medication. Five persons with prior history of malaria also relapsed, in spite of receiving weekly prophylactic medication during the transmission season. Their symptoms did not appear

TABLE 4 — *Prophylactic efficacy of hydroxychloroquine*
Incidence of malaria in subjects who received only weekly suppressive prophylactic medication

Group	Incidence of malaria	
	Suppressive medication only (65)	Non-medicated controls (154)
Subjects with no history of prior malaria	0/23	66/ 76 (87 %) (*a*)
Subjects with recent history:		
Attacks during transmission season after missing doses for > 3 weeks	8/42 (19 %)	46/ 78 (59 %) (*b*)
Attacks only during six months post-medication period	5/42 (12 %)	0
	13/42 (31 %)	112/154 (73 %) (*b*)

(*a*) 2 occurred only during follow-up period.
(*b*) 18 recurred also during follow-up period.

until 122-151 days after the last dose. The remaining two cases were «primo» attacks in 7-year old children who neither had prior history nor evidence of malaria during the transmission season. They were examples of prolonged incubation period or latency (bottom table 1).

DISCUSSION AND COMMENTS

During the course of evaluation of hydrocychloroquine diphosphate under hyperendemic field conditions, 146 overt attacks of vivax malaria were treated in 137 individuals. The youngest patient treated was 10 months old and the eldest was 75 years of age. Symptoms of the disease abated within 24 to 48 hours. The drug was rapidly effective when given at an adult dose level of 1.5 gm in 2 days, or adjusted for age; but a single suppressive dose administered once weekly (0.5 gm per adult; 0.25 gm for 6-12 year old children, or 0.125 gm for 1-6 year old children) was insufficient for prompt control of fever in some cases. The doses administered were well tolerated in all instances, and treatment followed by 15 weeks of suppressive medication did not interfere with the normal course of the one pregnancy in the study group. The data on the 137 individuals treated for overt malaria are presented in table 3.

The efficacy of hydroxychloroquine as a suppressive drug for the management of relapsing vivax malaria was clearly shown. The exposure to malaria during the transmission season was intense as shown by the fact that 64 «primo» cases of malaria were observed during the season of active transmission. Twenty-three individuals who initially received only weekly suppressive medication and who gave no history of antecedent malaria, showed no evidence of malaria. This is especially noteworthy because of the fact that 7 of the 23 were in families which included controls who developed clinical malaria. Eight of a group of 43 individuals who gave a history of malaria within the previous year, and who initially received weekly suppressive medication but were irregular in taking the drug, developed clinical malaria 14 to 35 days after interrupting the suppressive regimen. All subjects promptly responded to treatment, completed the post-treatment course of suppressive medication, and showed no evidence of recurrence during the six-month follow-up period of observation. On the other hand, 5 members of the suppressive group with positive history who had complete freedom from symptoms during the transmission season, developed clinical malaria four to six months after the termination of suppressive medication.

It is apparent from the observations made during this study that the vivax malaria encountered in Sed el Boshrié resembles the St. Elizabeth and Korean types with respect to relapse intervals (9). It is interesting to note that not a single case of *P. falciparum* infection was encountered, although one of the subjects had been diagnosed as M. T. malaria by the WHO team two months before this experiment started, and was treated with chloroquine at that time. *Falciparum* malaria was prevalent in the region during World War II.

SUMMARY AND CONCLUSIONS

1. Hydroxychloroquine diphosphate has been evaluated as a therapeutic and suppressive agent against relapsing vivax malaria under hyperendemic field conditions at Sed el Boshrié, Lebanon.

2. One hundred forty-six attacks in 137 individuals were treated with satisfactory results. Symptoms of overt vivax malaria were rapidly controlled (24 to 48 hours) when the drug was administered at an adult dose level of 1.0 gm immediately, and 0.5 gm the following day. The dosage was reduced by one-half for children 6 to 12 years of age, and to one-fourth that amount for children under six. The youngest child treated was 10 months old.

3. Hydroxychloroquine diphosphate was well tolerated in all instances. At the dose levels administered the drug did not interfere with the normal course of pregnancy.

4. When administered in weekly doses of 0.5, 0.25 and 0.125 gm, according to age, hydroxychloroquine diphosphate prevented the appearance of relapse or superinfection, if medication was not interrupted.

None of twenty-three subjects, without previous history of malaria, who received only weekly suppressive doses, showed evidence of vivax malaria either during the transmission season or during the six-month follow-up period.

Of thirty-four subjects with prior history of malaria, none of those who regularly received suppressive hydroxychloroquine medication experienced attacks during the transmission season, but five developed overt malaria 121-151 days after the last suppressive dose.

5. There were 118 cases of malaria among 162 nonmedicated controls or subjects who were irregular in taking their weekly doses; the attack rate was 72.8 %. Among the 76 nonmedicated controls who had no history of malaria the attack rate was 87 %; the attack rate was 59 % among those nonmedicated controls who had had malaria within the preceding year.

6. It is concluded that hydroxychloroquine diphosphate is a highly effective, well tolerated, therapeutic and prophylactic suppressive drug for the management of vivax malaria under hyperendemic conditions. Because of its low degree of toxicity it is the drug of choice for parenteral therapy.

ACKNOWLEDGEMENT

The authors wish to acknowledge with grateful appreciation the assistance of Dr. J. Balikian of the Department of Parasitology of the American University of Beirut, Lebanon. We are equally grateful to Mr. M. K. Hadidian, who carried out the preliminary survey for us.

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GENERAL DISCUSSION

Dr. G. JEFFERY (U. S. A.) — In regard to the question concerning the freezing of whole mosquitoes, we have read with much interest of this technique. Although we have not yet tried such preservation of sporozoites in the whole mosquito it seems quite likely that it would be successful if the proper medium and freezing temperatures could be determined. This technique would appear to be specially desirable where it is desired to preserve material in the field or at a time when facilities or personnel were not immediately available. Dissections might then be postponed until a more convenient time.

Dr. D. BERBERIAN (U. S. A.) — *Question:* Dr. L. J. Bruce-Chwatt questioned the practical value of adding one more drug to the armamentarium of malaria and asked whether hydroxychloroquine was superior to chloroquine or amodiaquin as an antimalarial drug?

Answer: For the oral therapy and suppression of malaria hydroxychloroquine resembles other 4-aminoquinolines now used and superiority was not claimed. This report was on suppressive action but since the question of superiority has been raised we emphasize that the acute intravenous and intramuscular toxicity of hydroxychloroquine is only one-third that of chloroquine. We therefore believe that in cases of acute malarial fever, especially in malignant forms, when parenteral administration of an antimalarial drug becomes imperative, hydroxychloroquine should be considered as the drug of choice. Hoekenga (1953--1955) treated 26 acutes *falciparum* infections with intravenous doses of 0.36 gm of hydroxychloroquine diphosphate dissolved in 500 cm^3 of normal saline. He also treated 37 others by administering the same dose of the drug dissolved in 9.0 cm^3 of saline, via the intramuscular route.

He obtained excellent therapeutic results. The i. m. injections were not painful and he observed no untoward reaction.

Dr. L. BRUCE-CHWATT (U. K)

ZUCKERMAN — The speaker pointed out the importance of the work on relationship between the basophilic index of the erythrocytes and the density of the infection with *P. berghei* and *P. vinckei*. This work, which was also done previously on a smaller scale by other authors working with human malaria parasites, might be of great value for the understanding of the biochemistry of malaria parasites.

DEMINA — The speaker congratulated Dr. Demina on her excellent work which explained several points of immunology of parasitic infections, namely the dynamics of the inherited immunity from the mother to the child. There is little doubt that we are only beginning to understand this complicated process.

SWELLENGREBEL — The problem of true relationship between the haemoglobin and malaria infection is now being actively investigated in the laboratory and in the field. It is probable that the tempting hypothesis of balanced polymorphism between sickling and malaria has not been proved yet and any far fetched conclusions are premature.

BISHOP — The value of this investigation is very great since it shows that in the problem of resistance of malaria parasites to drugs we are dealing with essentially the same phenomenon as in the case of insecticide resistance. Mutant genes are selected and the frequency of the selected gene increases with the increasing selection pressure on the population. From practical point of view it means that the selection pressure will be at its highest, when the parasite density is high viz, in cases of acute malaria treated by those drugs which have the specific selective action. The dosage of the drugs involved would play a relatively minor importance in the selection mechanism.

General discussion

BRAY — From the point of view of malaria eradication Dr. Bray's work is of importance since it shows that in some exceptional circumstances we must take into account the existence of a parasite reservoir in higher apes.

BERBERIAN — This interesting account would have been more valuable if we had some comparative data on oxychloroquine and chloroquine and other 4-aminoquinolines.

SECTION 2

CLINICAL

1st session: *Wednesday, September 10th — 3.00 to 4.30 p. m. Room D*

The meeting was held under the Chairmanship of Dr. Martin D. Young.

The Rapporteur was Dr. R. Coatney and the Secretary was Dr. Raul M. Rocha.

The following papers were presented and discussed:

CHEMOTHERAPY OF MALARIA

Sir Gordon Covell, M. D., D. P. H.

Thirty years ago the only specific drugs available for the treatment of malaria were the cinchona alkaloids, of which the most widely used was quinine. In recent years this has been largely supplanted by a number of synthetic compounds, most of which owe their origin to the exigencies of war.

Most malarial attacks can be effectively controlled by quinine or cinchona febrifuge, and it is questionable whether any of the synthetic antimalarials now in use would have been evolved had not Germany been deprived of all sources of quinine during the first world war. It was the urgent need for finding a substitute for quinine that inspired the series of researches by German chemists leading to the development of the first synthetic antimalarial compounds.

At the time when this work was being planned, all attempts to synthesize quinine had failed. But Guttmann and Ehrlich (1) in 1891 had discovered that methylene blue stains and therefore presumably penetrates malaria parasites, and had recorded some abatement of symptoms in patients suffering from *vivax* infections to whom the dye was administered.

With these observations in mind, a team of scientists working at Elberfeld in Germany embarked on a line of research which was destined to have far-reaching consequences. They introduced a basic side chain into the formula of methylene blue, producing a compound with considerable activity against avian malaria. The attachment of a similar side chain to the quinoline nucleus resulted in the production of pamaquin (Plasmochin), the first synthetic compound with effective action against human malaria parasites.

Pamaquin has certain properties which quinine lacks. It is a causal prophylactic of *falciparum* malaria, destroys *falciparum* gametocytes and brings about a marked reduction in the relapse rate of *vivax* malaria. It proved however unsuitable as a substitute for quinine because of its relatively high toxicity, its action on asexual blood parasites being effective only at dangerously high dosage.

The German scientists therefore embarked on further studies; they attached the basic side chain which had been evolved for pamaquin to other heterocyclic nuclei and finally produced the acridine compound mepacrine (Atebrin).

This drug has a powerful destructive action on the asexual erythrocytic forms of all species of human plasmodia. It has all the antimalarial properties of quinine, and against certain strains of *Plasmodium falciparum* is considerably more active. It has however the disadvantage of turning the skin yellow, and of producing in certain individuals other undesirable side effects.

Mepacrine was used extensively as a prophylactic by the Allied Forces during the second world war. In the South-East Asia and South Pacific campaigns malaria was so effectively controlled by this means during the later stages that it ceased to be a problem of military importance, though it continued to take a heavy toll among the Japanese until the end of the war.

The German programme of research on synthetic antimalarials had not ceased with the production of mepacrine. Their aim was now to evolve a drug with equally powerful antimalarial properties without its disadvantages. Removal of the methoxy-bearing ring from the mepacrine molecule gave rise to chloroquine (Resochin), a member of the 4-aminoquinoline series. This drug was still in an experimental stage at the outbreak of the second world war, and preliminary tests in Germany had raised doubts as to its possible toxic effects on man. Subsequent investigations in America showed these fears to be unfounded and early in the post-war period it was adopted as the standard antimalarial for the United States Army.

Chloroquine has the advantage over mepacrine of not discoloring the skin; it is on the whole a more active drug and is less likely to produce unpleasant side effects. Jeffery (2) has reported that patients infected with a South Pacific strain of *vivax* malaria ceased to be infective to mosquitoes after treatment with this drug. Another of the 4-aminoquinolines, amodiaquine (Camoquin) has properties similar to those of chloroquine.

Thus, during the period between the two world wars, pamaquin, mepacrine and chloroquine, members respectively of the 8-aminoquinoline, acridine and 4-aminoquinoline series of compounds, were evolved in Germany by successive modifications of formula, stemming from that of methylene blue.

During the second world war, when the Allies in their turn were cut off from all sources of quinine, British chemists, adopting a new line of approach, evolved a biguanide compound, proguanil (Paludrine), which proved to have remarkable antimalarial properties. This drug acts on the pre-erythrocytic forms of *P. falciparum*; it has a suppressive action against all forms of malaria and inhibits the late sporogonic forms of the parasite, rendering gametocyte carriers non-infective to mosquitoes; it has a lower toxicity than any other antimalarial known, and can be produced at comparatively low cost. Its action on the asexual erythrocytic forms of the malaria parasite is however not sufficiently rapid for treatment of the clinical attack, and its principal value is in prophylaxis.

Another synthetic antimalarial of importance is pyrimethamine (Daraprim), a member of the diaminopyrimidine series. It was synthesized in the United States, though many of the biological tests were conducted in England. In most respects its action closely resembles that of proguanil, and it also appears to inhibit the exo-erythrocytic forms of the Chesson (South Pacific) strain of *vivax* malaria (3). It has no apparent effect however on the relapse rate of the Madagascar strain of *P. vivax* (4), which is either of African or Asian origin. Like proguanil, it is too slow in action on asexual blood forms for therapeutic use, and its chief value is in prophylaxis. It is active in very small doses and can be produced at relatively low cost.

During the recent war in Korea, a serious problem was created by the number of malarial relapses occurring among service personnel returning from that area. As mentioned earlier, pamaquin has a marked action in reducing the relapse rate in *vivax* malaria, but is highly toxic. Intensive researches conducted in America culminated in the production of primaquine, another of the 8-aminoquinoline series, which is claimed to be four times as active as pamaquin in the radical cure of *vivax* malaria, while the maximum tolerated dose is twice as high. Following its adoption as a routine method of treatment, the relapse rate in United States personnel returning from Korea dropped to less than one per cent.

Thus, in chloroquine, amodiaquine, mepacrine and quinine we now have effective agents for the treatment of the clinical attack in all forms of malaria. In primaquine we have a drug which greatly reduces the relapse rate without undue risk of toxicity. Proguanil and pyrimethamine are efficient and inexpensive drugs for prophylaxis and suppression and for limiting mosquito infection; should resistance to either or not of these compounds be encountered recourse may be had to one or other of the more active schizontocidal drugs, such as chloroquine, for suppression of clinical symptoms.

For treatment and protection of the individual, of armies in the field or of labour forces under disciplinary control, the drugs at our disposal are adequate. But in an eradication campaign on a nation-wide scale, particularly for dealing with residual foci or outbreaks due to reintroduction of infection after discontinuance of insecticidal spraying, chemotherapeutic measures may be called for. Mass distribution of drugs is fraught with many difficulties, and for this purpose it would be of great advantage to possess a drug which, *when administered in a single dose,* would completely sterilize any malarial infection without risk. Such a drug is not yet available, but certain commercial firms have attempted to attain the desired result by combining two compounds in a single tablet. Extensive field trials are necessary before it can be forecast how far these are likely to succeed.

The development and action of modern antimalarial drugs have been discussed in greater detail in a monograph sponsored by WHO (5). Since its publication there have been no major advances of practical importance in this field. Development of antimalarial drugs (and indeed of all others) is largely determined by economic considerations and commercial firms are naturally averse from embarking on researches requiring substantial further expenditure unless there is a clear indication that the resulting product will be greatly superior to those now in use.

Perhaps the most interesting recent work in this field is the synthesis of certain hydroxy-naphthalenes by Duffin and Rollo (6), who found them highly active against rodent, avian and simian malaria. In field trials in West Africa, one of these drugs (377 C 54) was shown to have a pronounced schizontocidal action against *P. falciparum, P. malariæ* and *P. ovale* infections (7).

Field trials have also been reported with various 4-aminoquinolines e. g., Propoquin (8) and Planquenil (9, 10, 11), but none of these seems to offer any significant advantage over chloroquine. Another drug which has been subjected to trial in East (12) and West (13) Africa, Malaya (14) and Mexico (15) is Azacrin, an acridine compound with an action similar to that of mepacrine. It seems unlikely that any such compound could compete successfully against the 4-aminoquinolines.

Several papers have appeared in Russian journals relating to field trials of Chinocid (Quinocide), an 8-aminoquinoline, said to be highly effective in preventing relapses of *vivax* malaria (16, 17). Its properties appear to be similar to those of primaquine.

Finally, mention may be made of attempts by Pinotti and his colleagues in Brazil (18, 19) to combat malaria among certain tribes dwelling in remote areas where local conditions preclude the spraying of houses with residual insecticides by adding chloroquine to the salt used in the preparation of food. It seems likely however that the usefulness of this measure will be limited to very exceptional circumstances.

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CHEMOTHERAPEUTIC AGENTS AND MALARIA ERADICATION

MARTIN D. YOUNG [1]

The principal method used for the eradication of malaria is that of residual insecticides. However, the development of resistance of some mosquitoes to insecticides has alerted malariologists to the necessity for increasing the tempo of malaria eradication programs, as well as using methods of reinforcing the insecticide program. In view of our present knowledge, the residual insecticides will continue to be the mainstay of the eradication programs, but there are conditions under which the use of drugs can play a most important part.

The use of drugs will be helpful in conditions such as the following:

1. Under conditions where residual insecticides are inapplicable or ineffective, such as nomadic tribes, dwellings without walls, extra domiciliary transmission, migratory labor, absorption of insecticides on certain types of muds or adobes, and the behavioristic or physiological resistance of the vector to residual insecticides.

2. As a supplemental measure to residual spraying in order to hasten complete interruption of transmission in the early stages of a spraying campaign.

3. To reduce the foci of infection by achieving radical cure of all infections. One of the most important uses of the drug will be to eliminate the final infections when the eradication has been almost completed by the residual insecticides.

4. The use of drugs in the surveillance procedure to eliminate residual foci of transmission. This also stimulates the collection of blood smears as a routine part of the case-finding process on the theory that by giving the drug the patients will be more apt to submit to blood samples.

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Drugs are employed in many malarious countries, mainly as a supplemental measure, but in a few as the principal method of controlling or eradicating malaria. A total of 64 countries are known to be using drugs of plan to do so immediately (anonimous, 1957; Pampana, 1958). Of these, 27 are in the Western Hemisphere, 7 in Europe, and 15 in Asia. In Africa, where residual insecticides have been least successful, drugs will be tried in 10 countries.

TABLE 1 — *The relative sporontocidal action of drugs*

	vivax	*falciparum*
Quinine	—	—
Mepacrine	+	—
Chloroquine	×	—
Amodiaquine	+	—
Pamaquine	+	+
Primaquine	+	+
Proguanil, before resistance	+	+
Proguanil, after resistance	—	—
Pyrimethamine, before resistance	+	+
Pyrimethamine, after resistance	—	—

— = no sporontocidal effect
+ = sporontocidal effect
× = effect after appearance of parasite resistance to drug

The drugs may aid in several ways. By their sporontocidal action they may immediately interrupt the transmission of malaria from the infective human host, by radical cure they may prevent relapses, or by their ability to suppress the infection they may prevent or postpone the complete development of malaria in a patient who has been inoculated by a mosquito. The actions of the drugs in the above manners will be discussed below.

Clinical use of drugs — The use of drugs in treating the clinical attack is discussed in another paper by Sir Gordon Covell. This report will refer to the sporontocidal effect, viz., the interruption of the sporogonous cycle in the mosquito, of the therapeutic doses of drugs. In table 1, the relative sporontocidal action of drugs is shown against *Plasmodium vivax* and *P. falciparum*. So little is known on the other two species of human malaria that these are not included, although it is presumed that they would respond similarly to *P. vivax*.

The 4-aminoquinolines do not devitalize the mature gametocytes present. The gametocytes of *P. vivax* are removed from the blood stream as rapidly as the asexual forms and no new generations develop. Therefore, after one or two days the patient is not a source of infection. However, in *P. falciparum* the gametocytes may remain in the blood stream and infect mosquitoes for as long as three weeks after administration of the drug (Jeffery, Young, and Eyles, 1956).

Proguanil and pyrimethamine have the most rapid effect of all the modern drugs upon gametocytes, exerting sporontocidal effects within a few hours. The 8-aminoquinolines have an effect almost as rapid as the above two drugs.

Resistance by the parasites to drug action unfortunately may be exhibited against proguanil and pyrimethamine. This means that only the 8-aminoquinolines are safe to use without fear of resistance in areas where both *P. vivax* and *P. falciparum* are present. Where only *P. vivax* is present, the 4-aminoquinolines could be used.

Mass drug prophylaxis — The object of mass drug is to obtain suppressive, sporontocidal, and curative effects on existing infections, and to prevent the development of new infections. The dosages recommended by Covell *et al.*, in 1955, are as follows:

TABLE 2 — *Adult dosage of various drugs used for collective prophylaxis*

Drug	Communities with little immunity; armies in the field; etc.	Communities in endemic areas
Proguanil [1] [2] or	100 mg salt daily	200 mg salt twice a week, or 300 mg salt once a week
Chloroquine, or	300 mg base once a week	300 mg base once in 1-2 weeks
Amodiaquine, or	400 mg base once a week	400 mg base once in 1-2 weeks
Mepacrine, or	100 mg daily	200 mg twice a week, or 300 mg once a week
Pyrimethamine [1] or	25 mg once a week	25 mg once a week
Quinine [3]	650 mg (10 grains) daily	300 mg (5 grains) daily

[1] Contraindicated in areas where the prevailing malaria is known to be resistant to *either* of these drugs.

[2] A daily dose of 200 mg has been found necessary in parts of Africa.

[3] Recommended only when other drugs are not available.

Today, however, there are many different dosages being used varying from multi-daily intake in salt to monthly or even six-monthly treatments of large populations. In Africa where a very serious effort is underway with mass drug prophylaxis there are various schedules.

For mass chemoprophylaxis, quinine is the least effective of the group. Mapacrine is effective but because of frequent dosage necessary and toxicity it has been superseded. Proguanil has reduced malaria in many areas but the appearance of resistance has made it less useful. Pyrimethamine has given good results in many areas, for example, Vietnam (Farinaud and Choumara, 1954), French Morocco (Houel, 1956), Liberia (Miller, 1957), Nigeria (Archibald and Bruce-Chwatt, 1956), West Tanganyika (Clyde, 1957), Kenya (Roberts, 1956).

In Venezuela, Gabaldon (1958) gave 50 mgm weekly for six months to a population of 105,943. Six to eight weeks after suspension of chemoprophylaxis relapses occurred indicating suppressive cure had not been attained. There was no evidence of resistance. He believes that pyrimethamine is not capable of eradicating malaria, although it serves to interrupt the transmission. Resistance has occurred to the drug in Malaya and East Africa (see below). If this becomes widespread it will make the drug less useful.

The 4-aminoquinolines appear to be the most successful of the drugs to use as suppressives. They can reduce parasite rates dramatically, can suppress *vivax* and radically cure *falciparum* infections. They can be given weekly, and at least one, i. e., chloroquine, can be combined in table salt (see below). No significant resistance has appeared in the field to these drugs. At present these are the most useful single group of drugs.

As there have been no extensive trials of primaquine alone as a suppressive drug, no evaluation can be made. The possibility of frequent small doses being prophylactic is an interesting conjecture. Current work by the author in a few cases indicates that 30 mgm of primaquine weekly may quickly sterilize *P. vivax* and *P. falciparum* gametocytes and gradualy reduce the asexual parasitemia.

Drug combinations — For many years the combination of drugs, especially quinine and pamaquine, has been tried. Although effective to some extent, the shortcomings of each of the drugs in combination prevented this combination from becoming very effective in eradication programs. With the advent of the newer drugs, drug combination has become much more efficient.

In clinical malaria, schizontocidal agents such as the 4-aminoquinolines may be combined with the agents which destroy the tissue stages, i. e., the 8-aminoquinolines, for eradication of the infection. The sporontocidal effect of these combinations is rapid, as would be expected from the action of the individual compounds.

The combination of these drugs in suppressive monthly doses to protect against the spread of malaria was suggested by Walker (1955) as a result of a trial with Malayan school children. He reasoned that the 4-aminoquinolines quickly freed the blood stream of *falciparum* asexual parasites and interfered with the development of new generations of gametocytes and that a «gametocidal» drug would cause the circulating gametocytes to disappear. Recent work (Jeffery *et al.,* 1956; Burgess and Young, in press) indicates that gametocytes may be sterilized, although remaining in the bloodstream, after primaquine and pyrimethamine treatment.

Various trials of drug combinations as suppressives have been made or are underway. Miller (1957), in Liberia, found monthly doses of pyrimethamine in combination with chloroquine gave good results. Schneider *et al.* (1957), using half doses each of chloroquine and pyrimethamine found at first that it reduced the parasite rate but the effectiveness was lost after resistance to pyrimethamine developed. As no significant resistance has developed to primaquine, it appears that it may be combined with the 4-aminoquinolines, either chloroquine or amodiaquine, and given as a suppressive safely.

Drugs in salt — Pinotti (1954 *a* & *b*) proposed the use of chloroquine in salt as a prophylactic method. His laboratory and field experiments indicated that chloroquine was stable in salt, even if cooked, and that the daily intake of 45 or 30 mgm chloroquine in salt would suppress malaria in certain areas in Brazil (Pinotti, 1955). Recent experimental work by Coatney *et al.* (1958) confirmed the stability of chloroquine under conditions of storage, shipping, and food preparations, and showed the same to be true of pyrimethamine. They showed that weekly intake in salt of 300 mgm chloroquine or 25 mgm of pyrimethamine completely suppressed Chesson *vivax* malaria even though heavy infective dosages of sporozoites had been given. Malaria appeared after cessation of drug suppression, as follows: chloroquine, 33 to 43 days; pyrimethamine, 28 to 40 days.

According to the World Health Organization, Division of Malaria Eradication, there are plans to use the Pinotti drug-salt method in Ghana and in Cambodia (Pampana, 1956).

The question of drug resistance as related to this method presents itself. Because of the absence of any evidence of significant resistance of malaria to chloroquine under many varied conditions, it does not appear likely that resistance would arise from the drug-salt method.

The situation with pyrimethamine may be quite different. It has been shown experimentally that malaria parasites can develop resistance to small doses (Hernandez *et al.*, 1953) and to large doses of pyrimethamine (Young and Burgess, in press; Burgess and Young, in press). Furthermore, field experience has shown that when the drug is administered semiannually (Jones, 1954), monthly (Clyde and Shute, 1954), or weekly (Clyde and Shute, 1957), resistance may occur. Whether resistance would occur when the drug is taken daily in salt remains to be seen but it appears likely, especially when acute infections are challenged.

Another interesting point is whether a resistant strain, either to pyrimethamine or proguanil, can infect a person taken pyrimethamine regularly. It is known that proguanil-resistant *falciparum* can be transmitted to and develop in persons taking 100 mgm proguanil daily (Walker and Reid, 1953). Therefore, it appears likely that a person taking pyrimethamine might not be protected against a pyrimethamine-resistant strain.

Drug resistance — Although there have been suggestions of resistance of malaria to quinine, mepacrine, the 4-aminoquinolines, and the 8-aminoquinolines, no significant resistance in the field has ever been shown. This factor is not important in determining their value in malaria eradication programs.

There has been widespread resistance to proguanil reported. This has been so well documented and summarized by Covell *et al.* (1955), and by others that it is not necessary to review the evidence in detail here. Suffice it to say that it appears hazardous to use proguanil, in our present state of knowledge, on an eradication program where it is imperative to obtain predictable results.

Should the resistance be overcome by learning how to avert or neutralize the factor, the other attributes of the drug, such as being tasteless and its low cost, could make it very useful.

Resistance to pyrimethamine is being found in the field and experimentally. Jones (1954), following mass treatment of 100 mgm at six-month intervals to Kenya natives, found at the third mass treatment a high degree of resistance. *P. falciparum* infections were not eradicated by six times the usual dose. *P. malariæ* also showed a high resistance. Clyde and Shute (1954) after monthly, and in a later test after weekly treatments (1957), found *P. falciparum* resistant to the drug. Charles (1958) may have found resistance in Nigeria.

Schneider *et al.* (1957), using a combination of pyrimethamine and chloroquine in the North Camerouns, found resistance developed to the former which made the combination ineffective.

Young (1957) found that *P. malariæ* might exhibit initial resistance to the first treatment and could become higly resistant after one 100 mgm dose.

P. vivax and *P. falciparum* infections relapsing after exposure to single doses of pyrimethamine were higly resistant (Young and Burgess, in press; Burgess and Young, in press). The gametocytes were as resistant as the asexual forms and could readily infect mosquitoes following a dose of drug. The resistant character was persistent through trophozoite and sporozoite passages.

These field and experimental data leave little doubt that at least some strains of malaria can develop resistance rapidly to pyrimethamine. Resistance does not always appear after field use of the drug. Clyde (1957), not far from the area where first he found resistance, carried out another field experiment where no resistance was recognized. In many other areas of Africa there has been no resistance to pyrimethamine apparent, as follows: Belgian Congo (Vincke, 1954), Kenya (Roberts, 1956), Nigeria (Archibald and Bruce-Chwatt, 1956), Liberia (Miller, 1957), and French Morocco (Houel, 1956). Other areas also report no significant resistance, namely, S. Vietnam (Farinaud and Choumara, 1954) and Venezuela (Gabaldon, 1958).

Resistance is exhibited by both the asexual and the sexual parasites and apparently arises simultaneously. When this resistance occurs increased amounts of the drug do not prevent the parasite from being transmitted by mosquitoes which bite the patient. It now seems evident that in *P. falciparum* infections the resistance of the asexual parasites may be measured, even though they are not present in the blood stream, by reaction of the gametocytes to the drug. If the gametocytes will infect mosquitoes in the presence of drug, the asexual parasites will be resistant upon their reappearance.

Once established, the resistant character can persist through sporozoite transmission and trophozoite transmission. It is not altered by preservation at low temperatures. The persistence of the resistant character in the absence of contact with the drug is not known definitely but a clue may be indicated by a recent report by Clyde (personal communication of August 4, 1958). *P. falciparum* in the Mkuzi area, Tanganyika, was still resistant to pyrimethamine after 21 months but the resistance had been greatly reduced after 26 months.

SUMMARY

1. Although not the principal method of malaria eradication, drugs are used in most malarious countries to aid in the malaria programs.

2. Experimental and field information indicate that resistance can become important with proguanil and pyrimethamine.

3. The use of the 8-aminoquinolines for radical cures, and of the 4-aminoquinolines for clinical cures and for suppression appear to be the best selections.

4. The combining of drugs, especially chloroquine, in articles of food such as salt holds promise in certain areas.

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L'ASSOCIATION CHLOROQUINE/PYRIMÉTHAMINE DANS LE TRAITEMENT ET LA PRÉVENTION DU PALUDISME
RÉSULTATS D'UNE ÉTUDE DE 4 ANS

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Les associations médicamenteuses dans la thérapeutique du paludisme ont déjà fait l'objet de nombreux travaux. C'est Sinton (5) qui, associant quinine et Plasmochin, paraît avoir ouvert la voie à ces recherches dont les objectifs peuvent être les suivants:

1° — Agir, par deux médicaments différents, administrés simultanément ou successivement, sur les diverses formes ou stades d'évolution des plasmodium, c'est à quoi ont tendu les associations de médicaments schizonticides (atébrine, quinine, chloroquine, etc.) à des médicaments gamétocides (Plasmochin, Rhodoquine, Primaquine, etc.). Dans ce cas, la thérapeutique vise une action sur la division asexuée et sur les accès palustres par le produit schizonticide, alors que le médicament gamétocide est utilisé dans le but, soit d'interrompre la transmission cyclique du paludisme en détruisant les gamètes (action gamétocide) ou en les rendant non infestant pour le moustique (action antisporogonique), soit de prévenir les rechutes du paludisme à *P. vivax* en utilisant l'action des amino-8-quinoléines sur les formes exo-érythrocytaires secondaires du plasmodium responsable de ces rechutes.

2° — Obtenir le maximum d'effet avec un minimum de toxicité en cherchant à additionner l'activité antiplasmodiale de médicaments dont les toxicités sont différentes et qui ne s'additionnent donc pas. C'est cette idée qui a guidé Ph. Decourt lorsqu'il a associé, dans la Rodopréquine, deux gamétocides: la Plasmochin (ou Praequine) et la Rhodoquine (1).

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 140-149, 1959

Association chloroquine/pyriméthamine

Les recherches que nous poursuivons depuis de nombreuses années déjà nous ont permis de préciser l'activité de la chloroquine et celle de la pyriméthamine, à la fois dans le traitement curatif et dans la chimioprophylaxie du paludisme.

Nous considérons l'un et l'autre de ces médicaments essentiellement comme des schizonticides, en reconnaissant aussi leur action sur les gamètes de *P. vivax* et de *P. malariæ,* ainsi que l'activité antisporogonique de la pyriméthamine sur les gamètes de *P. falciparum* (2).

En associant pour la première fois, en 1954, chloroquine et pyriméthamine (3), notre objectif était uniquement d'ordre pharmacologique expérimental, car ni l'un ni l'autre de ces médicaments n'est toxique ou mal toléré lorsqu'il est employé aux doses actives. Nous nous proposions de voir si deux schizonticides, de mode d'action différent, additionnaient ou non leurs activités. On sait en effet que la chloroquine (comme l'atébrine et comme la quinine) agit sur les schizontes des plasmodium à tous les stades de la division asexuée, semblant bloquer les processus d'anabolisme au cours desquels les plasmodium en croissance métabolisent l'hémoglobine, alors que la pyriméthamine (comme le proguanil) n'a pas d'action sur la croissance des plasmodium et n'intervient qu'à un seul stade, au moment de la synthèse de la chromatine, bloquant la division cellulaire — ceci probablement en raison d'une action antifolique qui empêche la chromatine de répandre son acide ribonucléique dans le cytoplasme — ce qui fait que la pyriméthamine n'intervient sur la division cellulaire qu'au moment où la chromatine du trophozoïte âgé arrive au stade de division qui précède la formation du premier schizonte.

A priori donc, on pouvait se demander si l'association de ces deux médicaments était utile et si l'on observerait ou non une addition de leurs actions.

Cette expérimentation a été menée tout d'abord au laboratoire, sur *P. berghei* (plasmodium sensible à la chloroquine et à la pyriméthamine), puis en clinique humaine.

A) *Dans un premier temps,* nous avons étudié au laboratoire, sur des souris infestées par notre souche de *P. berghei,* l'association chloroquine/pyriméthamine; cette étude a été menée en utilisant nos tests habituels. Ces premiers résultats ont déjà été rapportés (3); nous les résumerons rapidement ici:

La chloroquine, employée seule à la dose de 2 mg/g répétée pendant 5 jours consécutifs à partir du deuxième jour de l'infestation, n'a pratiquement pas d'action sur l'évolution fatale de la maladie expérimentale de la souris.

La pyriméthamine, employée seule à la dose de 0,05 mg/kg répétée tous les jours pendant 5 jours consécutifs à partir du deuxième jour de l'infestation, n'empêche pas non plus l'évolution mortelle de la maladie.

Par contre, si l'on administre simultanément à des souris infestées de la même manière 2 mg/kg de chloroquine et 0,05 mg/kg de pyriméthamine pendant 5 jours consécutifs, on obtient, dès le troisième jour dans certains cas, et toujours le cinquième jour, la disparition des parasites, puis la guérison apparente de l'infection.

Ainsi, sur *P. berghei,* nous avons pu constater une évidente addition d'action des deux médicaments.

B) Encouragés par ces résultats expérimentaux, le *deuxième stade* de nos recherches fut consacré à l'étude de cette association dans le traitement d'accès palustres dûs à *P. vivax* ou à *P. falciparum.*

Pour se faire, nous avons utilisé des doses que nous considérons comme étant la moitié de la dose minima active employée en dose unique de ces deux médicaments, soit 0,150 g de chloroquine ou 0,025 g de pyriméthamine.

Ces médicaments ont été utilisés associés, aux doses indiquées ci--dessus, chez 21 malades, à l'hôpital Ernest Conseil, de Tunis, en 1954: 9 atteints de paludisme à *P. falciparum,* 12 à *P. vivax.* Les résultats obtenus ont été publiés à l'époque (3). Nous rappellerons que sur les 9 malades atteints de paludisme à *P. falciparum,* l'apyrexie a été obtenue en 1 jour, 33, et la disparition des schizontes en 1 jour, 55 — alors que pour les 12 malades atteints de paludisme à *P. vivax,* si l'apyrexie a été obtenue dans les mêmes délais (1 jour, 33), la disparition des schizontes a été un peu plus longue (1 jour, 62).

Nous avons constaté dans cet essai que l'association — comme il fallait s'y attendre — n'avait aucune action sur les gamètes de *P. falciparum,* mais que, par contre, elle agissait sur ceux de *P. vivax,* qui ont disparu en 2 jours, 41.

Les doses indiquées ci-dessus nous ont paru être les doses optima, car des doses inférieures de chloroquine (0,050 g ou, même, 0,100 g) associées à la même dose de 0,025 g de pyriméthamine, ont eu une action nettement plus lente, tant sur la fièvre que sur la disparition des schizontes. En particulier, l'administration de 0,050 g de chloroquine et de 0,025 g de pyriméthamine a été suivie de rechutes très rapides dans plusieurs cas de paludisme à *P. vivax,* ce qui montre bien que la dose de 0,025 g de pyriméthamine est nettement insuffisante et qu'il faut qu'elle soit associée à une dose optimum de chloroquine pour obtenir une action favorable.

De même, lorsque nous avons employé la dose de 0,150 g de chloroquine avec une dose plus faible de pyriméthamine (0,0125 g) nous avons observé aussi une action thérapeutique insuffisante et des rechutes précoces dans les cas de *P. vivax.*

Ces essais nous ont permis de démontrer que, dans le traitement de l'accès palustre chez l'homme, comme pour *P. berghei* chez la souris, les deux médicaments additionnent réellement leurs activités schizonticides, ce qui nous a amenés, dans *le troisième temps* de notre travail, à envisager l'emploi de cette association dans la prévention du paludisme (chimioprophylaxie).

C) *Ces essais de chimioprophylaxie* ont été menés au Cameroun, pendant les années 1956 et 1957.

Le choix des doses à utiliser a été basé sur les chiffres reconnus officiellement comme étant les doses actives en chimioprophylaxie de l'un et l'autre médicaments:

Pour la chloroquine, la Conférence Africaine du Paludisme de l'O. M. S. à Lagos, en 1955, avait fixé comme dose active 300 mg une fois par semaine pour les sujets de plus de 12 ans, 150 mg pour les sujets de 6 à 12 ans, 75 mg pour les enfants de moins de 6 ans — et pour la pyriméthamine, 25 mg hebdomadaire pour les sujets de plus de 5 ans — 12,5 mg hebdomadaire pour les enfants de moins de 5 ans.

En prenant ces directives pour bases de notre expérimentation, nous avons fait préparer, pour nos essais, des comprimés contenant chacun l'association de la moitié des doses reconnues actives pour l'adulte, soit 150 mg de chloroquine base et 12,5 mg de pyriméthamine base. Etant donné que ces essais étaient faits chez des enfants de moins de 9 ans, nous leur avons administré, une fois par semaine, ½ comprimé, soit 75 mg de chloroquine et 6,25 mg de pyriméthamine.

Les premiers résultats de ces recherches ont fait l'objet d'une publication (4) dans laquelle nous avons rapporté que, dans une zone hyperendémique où aucune lutte anti-anophélienne n'etait menée, nous avions obtenu une réduction considérable des index palustres, comparativement à une zone témoin non traitée. En effet, alors que les index plasmodiques se maintenaient entre 69 et 60 % dans le secteur témoin, on assista à une baisse spectaculaire de ces index dans le secteur traité où ils tombaient de 67 % avant traitement à 13 % après deux distributions médicamenteuses, à 6 % après un mois ½ de traitement, à 2,3 % après 2 mois ½ de traitement, et à 0,3 mois ½ après le début du traitement.

Cette nouvelle expérimentation nous avait permis, une fois de plus, d'enregistrer l'addition remarquable d'activité antipaludique de la chloroquine associée à la pyriméthamine.

Apparition de la chimiorésistance

La suite de notre travail a été non moins instructive. En effet, alors que les index plasmodiques étaient tombés à 0 et que, parallèlement, les index spléniques étaient passés de 71 à 4 %, nous avons vu, dans les mois suivants, alors que les enfants continuaient à prendre régulièrement les médicaments, s'élever progressivement les index plasmodiques à 15, puis 27 %, suivis lentement par les index spléniques.

C'est pourquoi nous avons, les mois suivants, essayé d'apprécier la cause de cet échec secondaire, en supposant, dès l'abord, qu'il était probablement en rapport avec l'apparition d'une chimiorésistance vis-à-vis de la pyriméthamine, éventualité déjà connue et que nous redoutions. Pour vérifier notre hypothèse, à partir du sixième mois (1er octobre 1956) et pendant les 15 mois suivants, nous avons modifié le protocole expérimental en divisant les 250 enfants en trois groupes égaux:

— L'un continuant à recevoir le même traitement hebdomadaire que précédemment: 75 mg chloroquine-base + 6,25 mg pyriméthamine-base;

— Le deuxième recevant 25 mg hebdomadaire de pyriméthamine, soit le double de la dose reconnue active pour l'enfant à la Conférence de Lagos;

— Le dernier groupe enfin recevant 300 mg hebdomadaire de chloroquine, soit, ici encore, le double de la dose active chez l'enfant.

L'ensemble des résultats est rapporté dans le tableau ci-joint, où l'on voit que la suite de l'observation montra que les index plasmodiques se sont maintenus à des taux relativement élevés dans le secteur traité par l'association chloroquine/pyriméthamine; ces index s'élevaient au-dessus de 10 % pendant les deux mois suivants, puis se sont abaissés légèrement jusqu'à 7 % avant la saison des pluies, pour s'élever à 35 % au moment de la recrudescence anophélienne (juillet à septembre), après laquelle ils se sont maintenus, les mois suivants, aux chiffres de 17,9 %, 20,5 %, 10,8 %, 7,9 %, etc.

Dans le groupe traité par la pyriméthamine à la dose double de la dose reconnue active, on constata, de même, une insuffisance notable de l'action de la prophylaxie: l'index plasmodique s'éleva à 30 % deux mois après le début du traitement, s'abaissant légèrement les mois suivants (15, 12, 10 %) pour remonter à 17 %, puis redescendre et atteindre à nouveau 21,8 % au moment de la recrudescence anophélienne; au moment le plus bas, le chiffre ne s'abaissera jamais au-dessous de 6 %.

Par contre, dans le groupe traité par la chloroquine, on a observé une action nettement plus favorable de la prophylaxie: l'index plasmodique s'est abaissé progressivement à 10, 6, 4 %, pour tomber à 0 au 5ème mois du traitement par la chloroquine seule; il s'éleva légèrement à nouveau aux 7ème et 8ème mois (6 et 5 %) pour retomber à 0 au 9ème mois. Au maximum de la transmission anophélienne, il atteindra 13 %, pour retomber rapidement à 2,9 % le 31 décembre, après 15 mois de traitement.

Ainsi, après 15 mois de traitement, les chiffres des index s'établissent de la façon suivante:

— Pour le groupe des enfants traités par l'association chloroquine/pyriméthamine, l'index plasmodique est à 7,9 %;

— Pour le group traité par la pyriméthamine, il est à 6,1 %;

— Pour le groupe des enfants traités par la chloroquine, il est à 2,9 %.

Certes, dans aucun cas il n'a été possible d'obtenir une réduction à 0 des index plasmodiques; ceci n'est guère pour nous étonner, dans un pays de paludisme hyperendémique où la distribution des comprimés n'a pas pu être faite de façon absolument régulière chaque semaine.

Cette expérimentation nous a surtout permis de constater l'apparition d'un certain degré de chimiorésistance vis-à-vis de la pyriméthamine; cette résistance ne paraît pas s'être accrue au fur et à mesure du développement de l'expérience. Il semble que ce soit, dans la plupart des cas, les mêmes enfants chez lesquels on a retrouvé des parasites dans le sang, ce qui tendrait à prouver que la résistance n'est pas globale et qu'il n'y a pas eu, jusqu'à présent, de transmission importante des souches résistantes à la pyriméthamine. Il ressort cependant de nos recherches que l'emploi de doses insuffisantes de pyriméthamine a provoqué l'apparition assez rapide d'une résistance à ce médicament, résistance qui n'a plus été vaincue ultérieurement lorsqu'on a employé une dose élevée de pyriméthamine.

En conclusion — Après cette série d'essais nous estimons que, malgré une indiscutable addition d'activité de ses composants, l'association chloroquine/pyriméthamine n'est pas à retenir en pratique dans le traitement du paludisme, pour les raisons suivantes:

1 — Le bénéfice thérapeutique résultant de l'association dans le traitement de l'accès palustre est sans intérêt, car on peut obtenir une action aussi rapide et aussi décisive en employant la dose optimum de chloroquine en une fois, et ceci sans aucun risques de toxicité.

2 — En chimioprophylaxie, l'intérêt principal eut été la possibilité d'associer une faible dose des deux médicaments dans l'espoir d'agir, non seulement sur les formes asexuées responsables des accès et, donc, sur la morbidité palustre, mais aussi sur la transmission du paludisme en utilisant l'action antisporogonique de la pyriméthamine, mais l'échec partiel que nous avons enregistré, apportant une nouvelle preuve de la création de souches résistantes à la pyriméthamine, doit inciter à une grande prudence dans l'emploi de ce médicament dans les campagnes de chimioprophylaxie de longue durée.

A notre avis, quand la lutte par les médicaments est menée pendant longtemps dans une même région, il faut éviter d'employer des produits qui risquent de créer une résistance, car même si ces médicaments sont administrés à des doses adéquates — ce qui n'empêche pas toujours l'apparition de la résistance — certains sujets échappent aux distribu-

TABLEAU DES INDEX PLASMODIQUES

Relevés chez les enfants de moins de 9 ans du village de Guirvidic (Diamaré, nord-Cameroun) pendant toute la durée de la campagne de chimioprophylaxie

	1956								
Dates	12.4	30.4	30.5	30.6	30.7	30.8	30.9	30.11	30.12
GROUPE A *									
Association chloroquine 75 mg/pyriméthamine 6.25 mg	67 %	13 %	6 %	2,3 %	0	15 %	27 %	21 %	16 %
GROUPE B									
Pyriméthamine seule 25 mg	—	—	—	—	—	—	27 %	30 %	15 %
GROUPE C									
Chloroquine seule 300 mg	—	—	—	—	—	—	27 %	10 %	6 %

	1957										
Dates	30.1	28.2	28.4	30.5	30.6	31.7	31.8	28.9	25.10	25.11	30.12
GROUPE A *											
Association chloroquine 75 mg/pyriméthamine 6.25 mg	16 %	14 %	15 %	8,5 %	10 %	7,8 %	35 %	17,9 %	20,5 %	10,8 %	7,9 %
GROUPE B											
Pyriméthamine seule 25 mg	12 %	10 %	17,5 %	10 %	6 %	11,9 %	21,8 %	12,8 %	18,4 %	8,3 %	6,1 %
GROUPE C											
Chloroquine seule 300 mg	4 %	0	6 %	5 %	0	3,3 %	5,4 %	12 %	13 %	5,7 %	2,9 %

* Début de distribution hebdomadaire des médicaments immédiatement après l'index du 12.4.56.

Du 12.4 au 1.10.56, tous les enfants reçoivent, une fois par semaine, 75 mg de chloroquine + 6.25 mg de pyriméthamine associés dans le même comprimé.

A partir du 1.10.56 et jusqu'au 31.12.57, l'ensemble des enfants traités est divisé en 3 groupes égaux:
— Le groupe A continue à recevoir la même dose de l'association chloroquine/pyriméthamine.
— Le groupe B 25 mg de pyriméthamine-base hebdomadaire.
— Le groupe C 300 mg de chloroquine-base hebdomadaire.

La période de juin à septembre correspond à la saison des pluies et à une recrudescence de la densité anophélienne.

tions et reçoivent, de ce fait, des doses insuffisantes, réalisant ainsi les conditions expérimentales optimum de la création de cette résistance.

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PHYSIOLOGICAL DEVELOPMENTS (INCLUDING SHOCK) IN MALARIA: ORIGIN AND TREATMENT

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The protean effects of mammalian malaria and the common lack of correlation between the intensity of infection (in terms of parasites) the pathological findings and the clinical state, have led us over the past decade to study some of the pathological processes involved.

We have tried to determine what changes in the physiological and structural make-up of the host are initiated by the parasite and *vice--versa:* how these changes are produced; how much of the picture is specific to malaria, and how much nonspecific. Finally, we have tried to find some indication of the missing link between the parasite in the erythrocyte and the host (Maegraith, 1948, 1951, 1954, 1956).

In what follows I have outlined some of the results of this work.

1. THE HOST

i) *Anaemia and oxygenation of host tissues*

Although the host tissues are quickly and severely disturbed in malaria in a way which suggests some anoxic mechanism, the anaemia and associated anoxaemia seldom become physiologically significant *per se*. If this is the case, is the carriage of oxygen to the tissues impeded in some other way?

We have studied this point in human, simian, and rat malaria and have found in all that the uptake and discharge of oxygen (as measured *in vitro*) are unaffected so long as the haemoglobin molecule itself remains unchanged (Maegraith, Jones and Andrews, 1951; Jones, 1951).

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 150-165, 1959

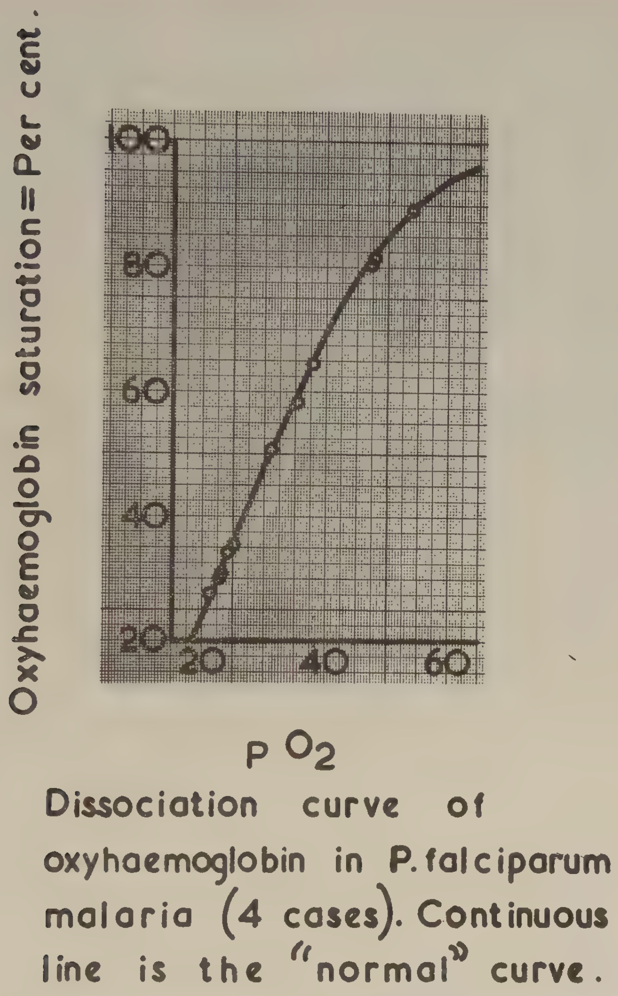

Fig. 1 — Dissociation curve of oxyhaemoglobin in *P. falciparum* malaria

Moreover, the physicochemical anatomy of the plasma does not alter enough to deviate the oxyhaemoglobin dissociation curve significantly, except occasionally to the right, in the terminal stages of very severe infections, thus facilitating rather than retarding the discharge of oxygen (Rigdon, 1954).

Inert pigments such as methaemoglobin are not found in the blood in malaria, although they may appear in the urine (produced in the kidneys from haemoglobin filtered from the plasma). Thus, despite the destruction of haemoglobin in the parasitized cells and its conversion by the parasite to inert haemozoin (through combination of haematin and denatured protein), there remains enough unchanged haemoglobin circulating in the surviving erythrocytes in all except the most fulminating infections to ensure oxygenation of both parasite and host (Deegan and Maegraith, 1956 *a* and *b*).

Erythropoiesis and haemoglobin synthesis are also not significantly disturbed.

The synthesis of haemoglobin appears to proceed vigorously. This was well illustrated in our recent studies of the distribution of radioactive iron in *P. berghei* infections in rats, in which we found that the iron derived from the haemoglobin of Fe^{59}-tagged erythrocytes destroyed during the initial waves of parasitaemia, was very rapidly returned to the circulation. Since the iron incorporated in haemozoin is unavailable for haemoglobin synthesis, the rapid turnover which we observed in the tissues of infected animals indicated that other sources of radio-iron were readily available. In view of the small reserves of Fe^{59} observed in the tissue stores, this supply must have derived from the haemoglobin of uninvaded erythrocytes destroyed by lysis or phagocytosis during the active infection (Deegan and Maegraith, 1958).

ii) *The circulation of the blood*

In malaria, the circulation may fail as a whole, with the development of medical shock, or it may fail locally. Local failure may develop with or without concomitant shock.

a) *Local failure* — Our early studies of the gross pathological effects of blackwater fever and malaria led us to point out that changes in the circulation were responsible for some of the physiological and structural patterns observed in the tissues and that many of these were non-specific to the parasitic infection as such, but dependent on the physiology and anatomy of the local blood vessels.

Analysis of some 200 cases of blackwater fever seen in West Africa during the war, demonstrated that the then current theory that precipitation of haemoglobin products caused terminal urinary suppression was untenable. We suggested instead that the secretion of urine failed because the blood flow through the glomerular vascular bed became temporarily inadequate, and posited some redistribution of intrarenal blood flow which rendered the cortex relatively ischaemic. This phenomenon was labelled at first the «tubular-vascular» syndrome, and later, when it became obvious that a similar picture developed in many other acute medical and surgical states, «renal anoxia» (Maegraith, 1944); Maegraith *et al.*, 1945).

Subsequent work by others has confirmed the reduction of renal blood flow in shock in man and experimental animals, and it is now generally accepted that, whatever the detailed mechanism, this syndrome of renal failure (now labelled with a variety of physiological and anatomical tags) arises from local vascular disturbances and can be initiated reflexly by extra- or intra-renal stimuli, including gross interference to renal function, for instance by the excessive administration of alkali, once recommended for the treatment of anuria in blackwater fever and now fortunately abandoned (Army Malarial Research Unit, 1945).

The important point to note is that this syndrome is primarily vascular in origin, emphasizing the often unappreciated fact that the components of the circulation in a particular tissue are as specific and important to the organ as, say, its secretory mechanisms.

This is particularly true in the case of the liver, in which centrilobular changes often arise in malaria, blackwater fever and many other acute medical states (Maegraith *et al.*, 1947). It is now generally agreed that the final picture of such centrilobular damage derives from interference with lobular blood flow which renders the centre ischaemic but not the periphery. Opinion as still divided as to the mechanism involved. Mechanical obstruction arising from swollen parenchymal cells or from intrasinusoidal accumulation of sludged blood cells, macrophages, swollen Kupffer cells, and so on, may sometimes, as in carbon tetrachloride poisoning, interfere with the lobular drainage, but there is good evidence that a more important process is constriction of the hepatic veins, leading to dynamic interference with the lobular drainage.

The full development of tissue damage in the central region is dependent not only on the degree of local circulatory failure but on

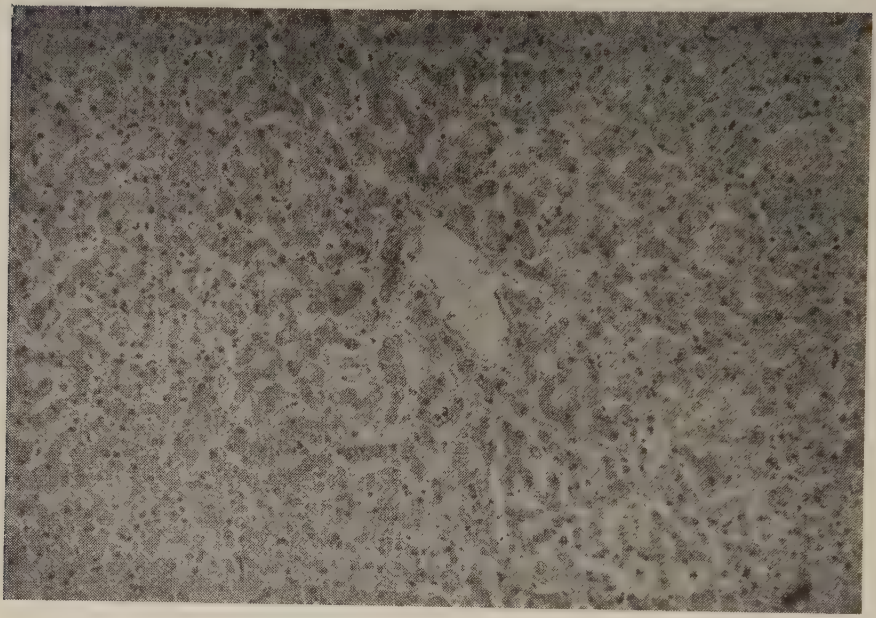

Fig. 2 — Centrilobular changes in the liver in *P. falciparum* malaria

other factors, including the oxygenation of the circulating blood, the time over which the changes in flow continue and metabolic effects already induced in the cells by the disease. The differential failure of the central tissues and the survival of the peripheral is also related to the prevailing intrahepatic circulation and circulatory pathways. Our own contributions to this subject have been reported at length elsewhere. They illustrate how investigations of pathological processes inevitably lead first to the study of the normal (Himsworth, 1947; Child, 1954; Maegraith *et al.*, 1949; Andews *et al.*, 1949, 1955).

I have mentioned only two examples of local tissue effects induced by circulatory disturbances. There are, of course, many others, for instance, the production of stasis in the brain. Time does not permit discussion of these. In some instances, moreover, the whole bodily economy may be disordered by such local changes. Thus, variations of blood flow in the endocrine glands, often with no obvious anatomical counterpart, may result in profound general effects, involving, for instance, the whole adrenal-pituitary complex.

For example, the experiments of Mercado and von Brand (1957) suggest that some adrenal cortical hormonal deficiency may be responsible for the failure of conversion of glucose into glycogen in the liver in severe *P. berghei* infections, since glycogen formation is maintained only in the presence of added cortisone. In advanced *P. knowlesi* malaria, on the other hand, we have observed glycogen synthesis without added cortisone (although somewhat better with cortisone) provided sufficient glucose is available, suggesting that at this stage the enzymes synthesizing glycogen are still capable of functioning, but cannot keep pace with the breakdown into glucose. In the absence of available glucose, the glycogen content of all tissues is depleted, suggesting that glyconeogenesis may also have failed. The findings in *P. berghei* infections are not reflected in any anatomical changes in the adrenals, except for some loss of cortical lipoids. Functional changes, however, may arise from local circulatory disturbances, upsetting the pattern of flow in relation to medulla and cortex. There is evidence that the overall adrenal flow is diminished in acute malaria and in medical shock, leading initially to excessive adrenaline secretion, with mobilization of both glucose and potassium. Mercado's results suggest that variation in cortical flow and associated hormone production or distribution may also occur at the height of an infection. Indeed, malaria may well be regarded as a stress syndrome. This point we are investigating. Other evidence of acute hormonal imbalance is accumulating. Thus, an increase in overall tissue fluid occurs in the host during *P. knowlesi* infection, associated with a fluctuating rise in plasma volume and with an acute reversal of this effect in the final stage of shock. Moreover, sodium tends to enter, and potassium leave, the erythrocytes during the infection.

b) *General circulatory failure* — Examination of the literature and of our own clinical and autopsy experience has convinced us that death in malaria, as in many other acute medical states, is associated not so much with heart failure as with circulatory collapse. Lesions undoubtedly develop in heart muscles, and in both human and animal malaria direct cardiac failure can occasionally be observed, but vascular failure or medical shock is the usual terminal event.

We have demonstrated this in recent experiments in *P. knowlesi* malaria by direct study of the circulatory dynamics in the terminal phases of the infection, in which the peripheral circulation is slowed, circulation time grossly retarded, systolic and diastolic blood pressures reduced and the return of venous blood to the heart greatly impaired. The condition is one of medical shock, with considerable pooling of blood in the peripheral vessels including those in the skin, which are dilated and filled with sluggishly moving blood. Constriction of these peripheral vessels can be achieved by pressor drugs, especially by noradrenaline, with rapid general restoration of the circulation. Similar shock can be demonstrated in other protozoan infections, for example in babesiasis (canine) with the same ready response to noradrenaline (Maegraith *et al.*, 1957).

The remarkable effects of this drug in restoring the circulation in malarial shock (*P. knowlesi*) will be seen in the cine film we are showing elsewhere.

Even the terminal stage of this shock is essentially reversible, and in animals in which the shock has been overcome, prevailing local lesions are equally reversible. This strongly emphasizes the essentially physiological nature of the origin of the clinical picture.

Time is a vital factor here, for reversible states will ultimately become irreversible and give rise to the patterns so dear to the morbid anatomists, seen, for instance, in the brain — the haemorrhages, clots and necrosis which I myself cannot accept as anything but the final and irreversible pathological outcome of processes which at an earlier stage were physiological and reversible (Maegraith, 1956).

iii) *Other effects*

Other gross disturbances of normal economy also occur in malaria. Albumin synthesis is reduced, sometimes very considerably. Lipoid metabolism is disturbed. If the host recovers from the acute stages of the infection, increased synthesis of globulins, especially of the γ-globulin takes place, contemporaneous with the appearance of humoral immune bodies and specific phagocytosis, indicating some host tissue response to antigens derived from the parasites themselves. There is also evidence that auto-antibodies are formed in the host from tissue damaged directly or indirectly by the parasite (Overman, 1951).

Lysis of the infected erythrocytes occurs at schizogony. Uninfected cells are also destroyed in the circulation, sometimes in enormous numbers. In some infections lysis is the dominant feature of the clinical picture; in others, in which the circulating erythrocyte mass may be equally reduced, it appears to be relatively insignificant. In *P. knowlesi* infection, studies with erythrocytes containing radioactive haemoglobin (Fe^{59}) have revealed that in a given animal the infection is either «lytic» or it is not.

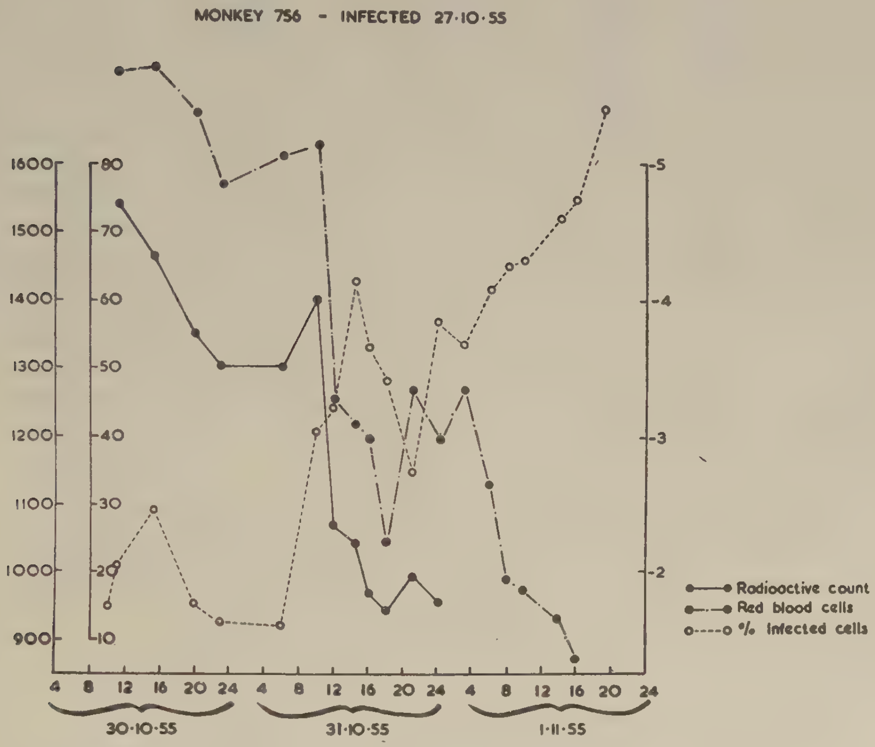

Fig. 3 — «Lytic» curve of circulating erythrocyte mass in *P. knowlesi* malaria. Note the abrupt fall during lysis

Erythrocytes from lytic infections are labile *in vitro* and are lysed readily when introduced into normal circulations or exposed to homologous tissue; those from non-lytic infections are not (Maegraith *et al.*, 1943). Normal tagged erythrocytes introduced into infected circulations behave like the homologous cells. Plasma from lytic cases fails to inhibit the latter reaction and may be actively lytic to normal cells. Thus in

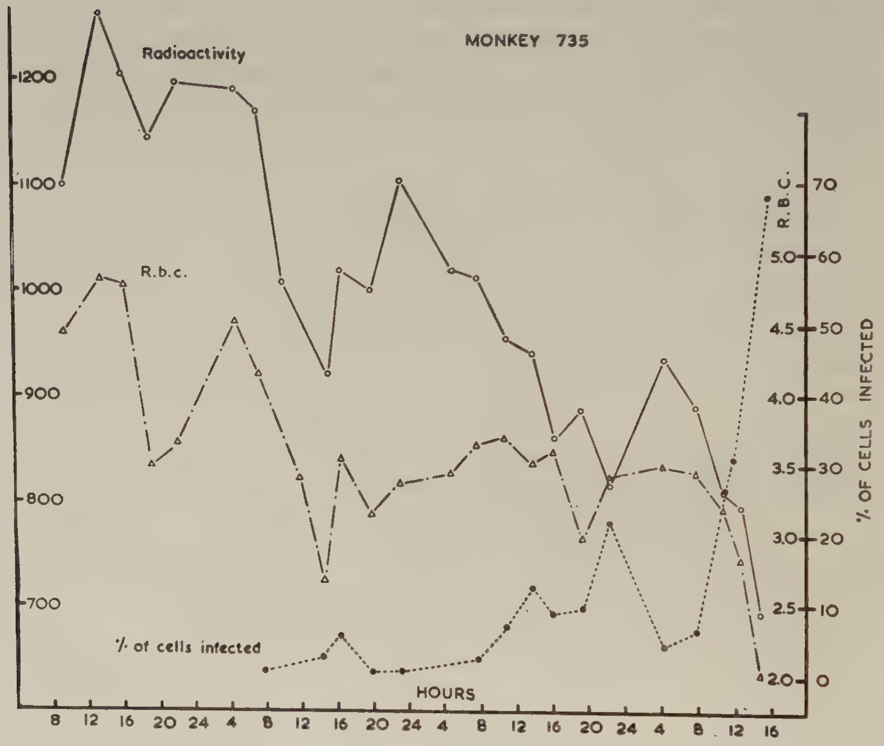

Fig. 4 — «Non-lytic» curve of circulating erythrocyte mass in *P. knowlesi* malaria. Note the «rise-and-fall» in relation to schizogony

lytic cases there is some change towards lysis in both the erythrocytes and their plasma-tissue environment.

In non-lytic infections radioactive and histological studies have demonstrated that tissue phagocytosis is the dominating factor in removal of erythrocytes. During shock pooling in the static peripheral circulation also effectively reduces the circulating erythrocyte mass.

Reference has been made above to the possible effects of the infection upon the acceptance of oxygen by tissues. In a series of crude experiments in *P. knowlesi* infections, using homologous liver tissue homogenates, we found differences in the oxygen uptake of tissue from normal and infected animals, suggesting that the mitochondria of the latter might be damaged. Studies of the cytochrome systems and relevant

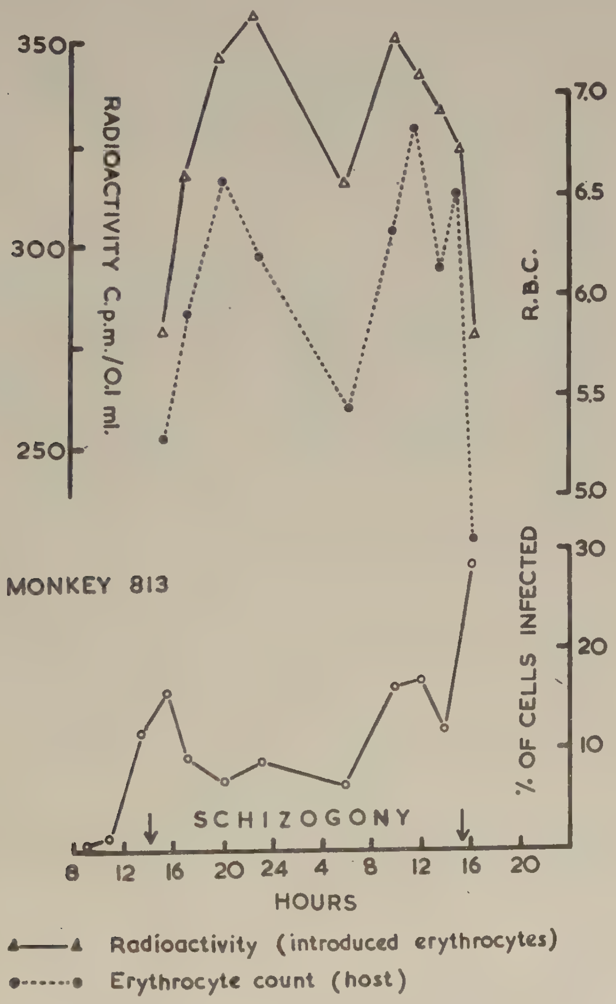

Fig. 5 — Radioactive erythrocytes introduced into the infected circulation in *P. knowlesi* malaria. Note the parallel curves for circulating erythrocyte mass in both introduced and host cells

parts of the Krebs cycle are now in progress. Herein may lie the key to tissue damage, for, whereas disturbances of such systems may be minimal and in themselves insufficient to affect the basic activity of tissues such as liver parenchyma, other concomitant factors, including reduction in oxygen supply initiated by local circulatory changes, or lack of substrates, excess of bilirubin, etc., may render them significant, and, given the time, lead to irreversible cellular damage.

2. THE PARASITE

So far as they can be ascertained the metabolic processes of the malaria parasite are similar to those of the specific hosts.

Energy exchange continues over parasitic growth and division during which the rate of oxygen consumption is prodigious. The tremendous metabolic activity of the growing parasite suggests an accessibility of enzymes so great as to indicate that they must be concentrated in small particles rather than in mitochondria. Cyanide inhibits the take-up of oxygen, indicating that the final pathways include heavy metal catalysts, similar to those of the host.

Of necessity, study of parasite respiration has been carried out either in infected whole blood or washed cells, or in parasites freed from their containing erythrocytes. In the final issue therefore the parasites have been studied outside their natural environment. This is particularly important in the case of *P. berghei,* which differentially invades reticulocytes, which have themselves similar metabolic pathways. Just how much the parasite is dependent on the host cells and *vice-versa* we do not yet know. We have to assume for the meantime that the tempos and direction of the metabolism of the host cell *per se* are not radically altered during the growth of the parasite (Maegraith *et al.*, 1951).

The conception of a busily metabolizing parasite multiplying within an erythrocyte naturally raises the question of direct competition between the two for available materials.

So far as oxygen is concerned, such competition is negligible.

This is not so, however, with certain substrates, for example, glucose. Thus, if the fate of available glucose over a given time is calculated in *P. knowlesi* malaria during heavy parasitaemia, it is found that the glucose consumed by the parasites is considerable in terms of that used by the host tissues (as distinct from that converted into glycogen).

Mobilization of glucose from both host and parasite is vigorous at this stage, and in some avian and mammalian malarias, liver and muscle

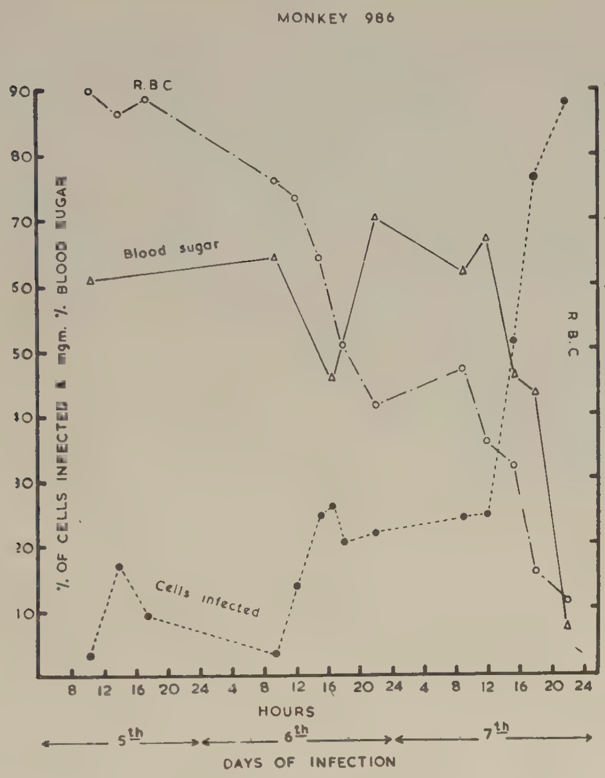

Fig. 6 — Blood sugar in *P. knowlesi* malaria. Note remarkable final drop in concentration (contemporaneous with depletion of liver and muscle glycogen)

glycogen may be practically depleted in the terminal stages (Maegraith, 1948; Devakul, 1958).

The parasite may also compete for substances other than glucose which cannot be supplied directly by the host cell, including methionine, p-aminobenzoic acid, phosphorus and calcium. The degree of competition must be studied in each individual case. As we have seen, in the case of glucose it is considerable and tends to favour the parasite. With other substances the reverse is true and the parasite appears at a disadvantage. Thus, if the host is given an exclusive milk diet the development of *P. knowlesi* and *P. berghei* (and also *P. vivax*) is retarded.

Administration of p-aminobenzoic acid (or methionine) restores parasitic multiplication. The balance between parasite and host can thus sometimes be disturbed by interfering with the nutrition of the host. The failure of parasites to multiply in the host on a milk diet, and the reversal of this effect by p-aminobenzoic acid has taught us nothing new about the metabolism of the parasite itself, but it has indicated that such metabolic processes may be studied *in vivo* with the parasite in its natural environment, i. e., in the invaded erythrocyte. It also emphasizes a significant point, so often overlooked, that parasite-host relationship is a two-way affair, for the parasite must accept the host just as much as the host the parasite (Maegraith *et al.*, 1952).

How are the metabolic processes of the parasite controlled in relation to its own life cycle? In this respect we have as yet little information, although a change in ATP/ADP ratio may occur in the late parasitic stages, suggesting alterations in energy transfer, and there is some evidence of the accumulation in infected cells of active inhibitory lipoid factors.

One further substrate must be mentioned. Haemoglobin is of great significance to the parasite, which uses the protein and converts the haematin into haemozoin. This is true so far as haemoglobin A is concerned. Is it equally true for other haemoglobins? Do these processes fail with haemoglobin S, for instance, which appears to confer some protection against *P. falciparum* infection? The recent work of Ingram, who has demonstrated a single aminoacid difference between the two haemoglobins, A and S, may be relevant in this respect.

3. PARASITE AND HOST

The final problem in the study of the pathogenesis of malaria is the mechanism of the interaction of parasite and host. How can we link the one with the other?

Examination of the physiological behaviour of the host at various stages of the infection, as outlined above, and described elsewhere indicates a direct link. This needs the conception of the initial operation of some substance or group of substances of nonspecific type, setting in train a series of interrelated and summating responses, metabolic, hormonal, circulatory and physiological.

The evidence in favour of such an interpretation of the whole picture of malaria is strong and increasing. Let me give just one example.

I have mentioned above the remarkable effect of noradrenaline in restoring the general circulation of the monkey in *P. knowlesi* shock. This results largely from the restoration of venous return to the heart following readjustment of the static peripheral circulation. In an attempt to discover whether direct action on the heart could also (even primarily) be involved, we compared the cardiac changes induced by the administration of the drug in the normal animal and in the shocked infected animal. In the former, injection of noradrenaline has a vigorous prolonged pressor effect and is associated with initial bradycardia, extrasystoles and deviations of the isoelectric levels of the E. C. G. These cardiac reactions can be completely abolished by atropine, without affecting the pressor action of the drug. Animals in shock, which respond clinically to similar doses of noradrenaline, show the pressor effect but

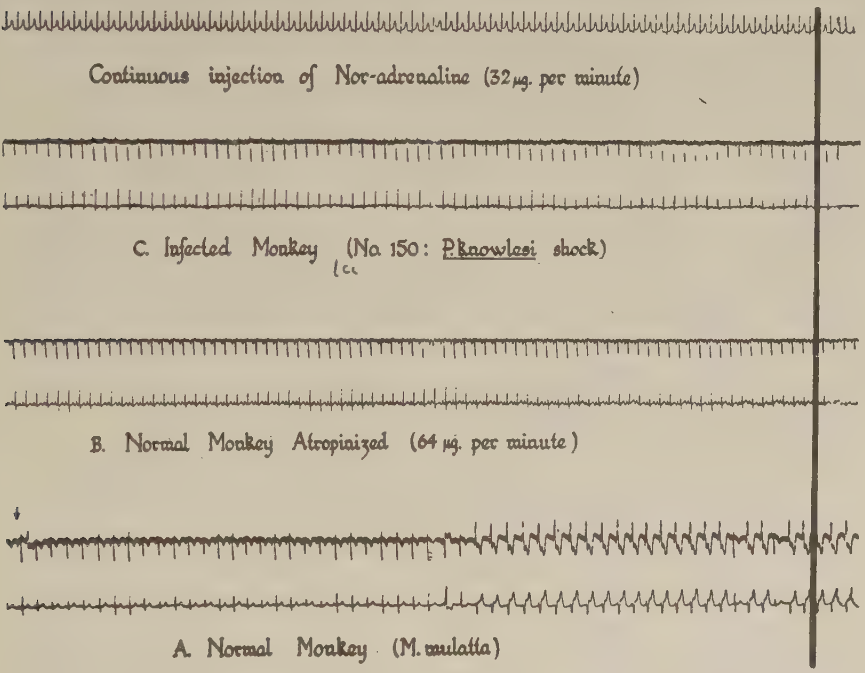

Fig. 7 — The effect of l-noradrenaline on cardiac rhythm and isoelectric levels. Note the «atropine-like» effect during shock

not the cardiac. This is true also of the response to the administration of adrenaline.

In cross transfusion experiments, in which the blood from a shocked infected animal was transfused into a normally reacting monkey, some depression of the cardiac response was demonstrated in the latter. The animal in malarial shock thus behaves in this respect as though it were under the influence of atropine. (This is not the case in other forms of shock. For instance, in human cardiac infarction shock, the direct effects of these drugs on the heart are present and even exaggerated.) (Maegrait, 1957; Littler and McKendrick, 1957.)

This could be explained by the presence of some humoral mechanisms.

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GENERAL DISCUSSION

Pr. B. Maegraith (U. K.) — Agents which Cameron and his colleagues have shown to damage mitochondria are apparently concerned with lipoids, for example, carbon tetrachloride. I think polipeptides and polisaccharides and lipoids-perhaps the fatty acid described by Laser may be involved.

Pr. J. Schneider (France) — La cause de la mort dans le paludisme est pour le Prof. Maegraith la stase vasculaire périphérique; cela est certain mais ne fait que reculer le problème. Quelle est la cause de cette stase, qui, rappelons, le est un symptome commum à divers etats de shock?

À notre avis cette stase est la conséquence d'une irritation du système nerveux qui, rappelons, peut dans le paludisme être provoqué par l'anoxie cérébrale secondaire à l'encombrement des capillaires du cerveau comme l'a montré expérimentalement J. Reilly provoque la vasodilatation périphérique cause de la stase et je pense qu'il faut rapprocher le shock grave des paludismes pernicieux du syndrome décrit par Reilly.

Dr. G. R. Coatney (U. S. A.) — In his interesting paper Sir Gordon Covell called attention to the American War effort toward the evaluation of antimalarial drugs. I want to say however that this effort was accelerated relative to the evaluation of the 4-aminoquinolines through our receiving in 1943 data from Dr. Jean Schneider, who spoke from this platform a few minutes ago, relative to his work with Sontochin in North Africa. Dr. Schneider's contribution has largely been ignored and I would like to take this opportunity to call it your attention.

Dr. Goodwin (U. K.) — It is possible that Sir Gordon Covells' experience with pyrimethamine and the Madagascar strain was a result of the ability of this strain to remain latent in the tissues for long periods. In a letter to the *British Medical Journal* (1953, *ii*, 392), Sir John Boyd

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pointed out that pyrimethamine exerts its action when the nucleus of the parisite is dividing, and that the exoerytrocytic forms of the Madagascar strain may remain latent for 30-40 weeks.

Possibly Dr. Gabaldon had a strain of this kind in Venezuela, and should have distributed pyrimethamine for longer than 6 months. So far, there have been no published reports on this campaign, and we have no figures of the number of relapses or information on the effectiveness of drug distribution or control of incoming people from untreated areas.

Strains resistant to pyrimethamine undoubtedly occur, and the paper by Dr. Ann Bishop this morning may help us to avoid selecting them. Dr. Trager's paper showed that, in certain circumstances, the malaria parasite is able to utilize folinic acid and should help to unravel the biochemical changes which occur in the resistant parasite. Pyrimethamine and proguanil act upon the biochemical patway which synthesizes folinic acid from p-aminobenzoate and a resistant strain manages in some way to avoid this pathway.

We now have a good variety of drugs to use in the eradication of malaria — schizonticides, sporonticides and insecticides — and there is no justification for relying on one alone. We should select the drug or drugs which are most likely to be the best for the particular eradication area, and be prepared to change if necessary. The limiting factors in the eradication of malaria are now money, personnel and communications.

Dr. Schneider's results with pyrimethamine and chloroquine do not greatly tell against this combination of drugs. It is not a good principle to rely upon half-doses of drugs which have such totally different modes of action. Experiments in our laboratory, in London, with our strains of *Plasmodium gallinaceum* and *P. berghei,* have not confirmed Dr. Schneider's view that the drugs are synergistic. The development of pyrimethamine resistence would be less likely if full doses were given, and such strains if they appeared, would not be perpetrated if the full dose of chloroquine were to be given at the same time. Dr. Schneider himself showed that the full dose of 300 mg of chloroquine was effective after some degree of pyrimethamine resistance had developed.

Dr. A. HENRY (Algérie) *Quinimax et Paludisme* — La réputation de la quinne n'est plus à faire, mais il semble que l'emploi des synthétiques fait un peu oublier ses bienfaits. Depuis l'avant guerre nous

sommes restés fidèles à un product appelé Quinimax (Laboratoire Derol) moins connu à l'étranger.

Tout en ayant à l'occasion recours aux synthétiques, nous tenons à insister sur cette realisation. Dans leur beau travail de l'OMS Sir Gordon Covell (et alliés) indique au sujet du mélange des alcaloïdes de quinquina l'efficacité essentiellement la même que celle de la quinine mais ne pouvant être administrés par voie parental et pouvant par voie buccale provoquer nausées et vomissements. Dans le quinimax les alcaloïdes sont actives et solubilisés en combinaison avec un phénel: la Resorcina — très bien supporté par la voie buccale et aussi remarquablement par la vois souscutanée ou intramusculaire. Jamais d'indurations — jamais d'obices. L'association réalisée permit l'emploi de doses moindres que les doses de quinine et dans les cas les plus graves (même pernicieux) on obtient de bons résultats.

Le Quinimax joint à ses actions spécifiques les actions paraspécifiques de la quinine, qui ont une importance sur les sujets récemment ou choroniquement infectés avec troubles organiques.

Terminons en signalant chez les chroniques l'heureuse influence des cures d'eaux minérales, qui, avec la chimiothérapie, réalisent ce que la chimiothérapie seul n'avait pu obtenir.

Pr. J. SCHNEIDER (France) — *Réponse au Dr. Goodwin* — Les conditions du laboratoire et de la chimique différent profondément, le Dr. Goodwin parait méconnaître un fait d'observation courante: celui de la prise irrégulière des médicaments par certains individus sumis à une chimioprophylaxis de longue durée. Tous ceux qui ont eu la responsabilité de campagnes de masse savent qu'une proportion non négligeable d'individus omettent pour raisons variées de prendre le médicament préscrit ou ne prennent qu'une fraction de la dose indiquée, ces individus se trouvent donc dans les conditions décrites dans notre communication où des doses insuffisantes ont determiné l'apparition de résistance. Le fait que cette résistance survient dans de telles conditions justifie notre prise formelle de position contre l'emploi dans des campagnes prolongées de chimioprophylaxis de masse de médicaments susceptibles de créer une chimio-résistance. Mon expérience de clinicien et d'épidémiologiste m'a convaincu de l'impossibilité qu'il y a d'exiger pendant des mois une stricte discipline dans la prise de médicaments et cette notion commande l'attitude du malariologue averti, qui doit prescrire pour telles campagnes un médicament non susceptible de créer quelques soient les aléas des prises médicamenteuses, un état de chimio-résistance.

Dr. M. D. Young (U. S. A.) — As to resistance to pyrimethamine, we now know little about it. We may all find ourselves in entire agreement.

2ND SESSION: *Thursday, September 11th — 3.00 to 3.40 p. m. Room D*

The meeting was held under the Chairmanship of Sir Gordon Covell and Dr. Jean Schneider.

The Rapporteur was Dr. R. Coatney and the Secretary was Dr. Raul M. Rocha.

The following papers were presented and discussed:

THE SINGLE DOSE TREATMENT OF MALARIA IN THE AMERICAN TROPICS

MARK T. HOEKENGA, M. D.
Puerto Armuelles, Panama

Five years ago, at the meeting of the Fifth International Congresses on Tropical Medicine and Malaria, in Istanbul, I reported on the results of treating 920 malaria infections with a single oral dose of either chloroquine, amodiaquin or hydroxychloroquine. Since then, in Honduras and in Panama, we have successfully managed several thousand clinical malaria infections with a single dose of an antimalarial drug. The majority were treated on an ambulant basis, but over 3000 were hospitalized for accurate records of fever, parasitemia, toxicity, treatment failures and relapses. These are the infections that I wish to report briefly today.

THE DRUGS USED

The first slide (Table 1) lists the drugs that we have employed in these clinical studies, and the total number of infections treated with each one.

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TABLE 1 — *Number of malaria infections treated*

	Oral	Parenteral	Total
Amodiaquin (Camoquin)	1,030	10	1,040
Chloroquine (Aralen)	857	300	1,157
Hydroxychloroquine (Plaquenil)	150	63	213
Pyrimethamine (Daraprim)	200	—	200
Propoquin	65	335	400
Total	2,302	708	3,010

The pharmacologic and clinical properties of the 4-aminoquinolines are too well known to necessitate repeating. The same is true of pyrimethamine. These drugs are the bulwark of malaria treatment all over the world, as is well known to this group. A few words on propoquin would be in order, however, since it is not as familiar as the other compounds. The next slide shows its structural formula, for comparison with other 4-aminoquinolines.

Thompson (unpublished observations) in 1952, found propoquin, used by the drug diet method against *P. lophuræ* infections in chicks, to be approximately 32 times as active as quinine in suppressing the parasitemia. Toxicity studies by Weston (unpublished observations) on albino mice, rats, rhesus monkeys and dogs, indicated excellent tolerance except in very high single parenteral doses or prolonged, high, oral doses. In tissue distribution studies, Glazko (unpublished observations) observed in rats, following oral dosage, that the drug is readily absorbed from the gut, reaches high levels in the liver, spleen, kidney and lung, and is slowly degraded or excreted.

MATERIAL AND METHODS

Except for a dozen North Americans, all 3,010 patients were Hondurans and Panamanians, representing various mixtures of Spanish, Indian and Negro ancestry. A wide span of ages was present in each of the treatment groups, from early infancy to the very elderly. The proportion of sexes was also similar in the groups, approximately 60 per cent being males and 40 per cent females. All of these individuals lived in the hot, humid lowlands where the United Fruit Company's banana plantations are located. In these areas, *Anopheles albimanus* is the principal vector and malaria is endemic all year, with slightly decreased incidence during the dry season. Because malaria is endemic, the adult native population may be considered to have acquired partial immunity to the local strain.

As soon as a diagnosis of malaria was confirmed by blood film, treatment was begun. Oral temperature on all patients was recorded every four hours. Approximately 300 chloroquine and 500 amodiaquin treated patients had thick blood films examined twice daily; in the remainder, as well as in all the patients treated with hydroxychloroquine, pyrimethamine and propoquin, thick blood films were examined every six hours. The amount of drug and the time of administration were not related to parasite density, to the stage of parasite cycle, or to the degree of fever. All groups were comparable in respect to degree of parasitemia when treatment was started.

RESULTS

In presenting the results, I will consider first the 2,302 individuals who received a single *oral* dose of one of the five compounds, and subsequently the 708 parenterally treated ones.

A. *Results with oral treatment*

In nearly all patients treated with an oral dose of one of the 4-aminoquinolines, headache, malaise, vomiting, joint pains and other symptoms caused by malaria disappeared within 36 to 48 hours and adult males were usually able to return to work by the fourth day after treatment.

The next slide (Table 2) tabulates the results obtained with various doses of amodiaquin or chloroquine. Dosage with amodiaquin ranged from 1.0 to 0.4 gm of base; the most common regimen being 0.6 gm (3 tablets). Note that in 401 *falciparum* infections, the average duration of fever was 18.8 hours and parasite clearance time 29.0 hours; for 344 *vivax* infections, these figures were 18.0 and 24.1 hours, respectively.

The most common chloroquine regimen was also 0.6 gm of the base (4 tablets); the average duration of fever in 388 *falciparum* cases was 19.2 hours, and parasite clearance time 29.2 hours; in 299 *vivax* infections, these figures were 17.9 and 27.1 hours, respectively. There seems not to be a significant difference between amodiaquin and chloroquine when duration of fever and parasitemia are thus compared. However, notice the figures in parenthesis which represent the number of patients in which the immediate response to the single dose treatment was *not* satisfactory; amodiaquine here appears to have an advantage over chloroquine.

TABLE 2 — *Immediate results of oral single dose treatment of malaria with amodiaquin or chloroquine*

Adult dose [2] (Gm. of Base)	*P. falciparum* infections			*P. vivax* infections		
	Number of patients	Average number of hours until		Number of patients	Average number of hours until	
		Temp. remained normal	Parasites disappeared		Temp. remained normal	Parasites disappeared
Amodiaquin (1,030 infections)						
1.0	33	13.2	26.3	42	15.3	27.5
0.8	40	18.5	34.6	40	14.6	25.6
→ 0.6	*401* (3) [1]	*18.8*	*29.0*	*344* (2) [1]	*18.0*	*24.1*
0.4	68 (1) [1]	20.0	31.6	62 (3) [1]	18.9	27.6
Chloroquine (857 infections)						
→ 0.6	*388* (6) [1]	*19.2*	*29.2*	*299* (12)[1]	*17.9*	*27.1*
0.45	80 (5) [1]	32.1	38.2	90	20.4	29.8

[1] The figure in parenthesis represents the number of patients in which the response to the single dose treatment was not satisfactory. These immediate failures to the single dose treatment are not included in the tabulation of the average number of hours until temperature remained normal nor the average number of hours for parasites to be cleared.

[2] Children under 12 years of age received proportionately less.

The next slide (Table 3) shows the same type of data for pyrimethamine, hydroxychloroquine and propoquin. It need only be pointed out that the two lesser-known 4-aminoquinoline drugs (hydroxychloroquine and propoquin) compare favorably with amodiaquin and chloroquine. Pyrimethamine generally produced less satisfactory results but it is well to remember that much smaller doses of pyrimethamine are employed.

It should be noted that gametocytes persisted in occasional cases, regardless of the regimen used; this is not included in tabulations presented.

The number of known relapses or late failures was small. There were 34 in all, and all had malaria due to *P. vivax*. Seven had been treated with 0.45 gm of chloroquin, eleven with 0.6 gm chloroquine, six with 0.4 gm of amodiaquin and ten with 0.6 gm of chloroquine. There

Table 3 — *Immediate results of oral single dose treatments of malaria with pyrimethamine, hidroxychloroquine or propoquin*

Adult dose [2] (Gm. of Base)	*P. falciparum* infections			*P. vivax* infections		
	Number of patients	Average number of hours until		Number of patients	Average number of hours until	
		Temp. remained normal	Parasites disappeared		Temp. remained normal	Parasites disappeared
Pyrimethamine (200 infections)						
0.1	64 (4) [1]	34.4	39.2	42 (2) [1]	32.3	34.1
0.05	54 (6) [1]	35.1	38.4	40 (4) [1]	39.1	36.3
Hydroxychloroquine (150 infections)						
1.25	70 (2) [1]	20.8	31.2	80	18.8	24.6
Propoquin (65 infections)						
0.6	29	27.1	27.3	36	23.7	33.9

[1] The figure in parenthesis represents the number of patients in wich the response to the single dose treatment was not satisfactory. These immediate failures to the single dose treatment are not included in the tabulation of the average number of hours until temperature remained normal nor the average number of hours for parasite clearance.

[2] Children under 12 years of age received proportionately less.

were no relapses reported among the hydroxychloroquine, propoquin or pyrimethamine groups.

In the dosages administered, no serious toxic effects were noted with any compounds. There was occasional nausea and vomiting following drug ingestion, a little more often with amodiaquin than with the others. Temporary dizziness was also alleged occasionally. These side effects never constituted a serious problem. All compounds were given to persons with malaria complicated by other conditions such as cardiovascular disease, marked malnutrition, hepatic or renal disease, pulmonary diseases, or advanced pregnancy. In no instance was there clinical evidence of drug toxicity or intolerance.

B. *Results with parenteral treatment*

So much for the oral medication. Now a few words about the results in parenterally treated cases.

Amodiaquine, in the form of the monohydrochloride, was given intramuscularly to only 10 individuals. The response, measured by temperature and parasitemia was satisfactory, but the compound caused such marked and persistent pain at the site of injection that its use was discontinued. The number of cases is too small to make tabulation worthwhile.

The other three compounds used (chloroquine, hydroxychloroquine, propoquin) generally produced a fairly rapid alleviation of muscle and joint pains, headache, malaise and other symptoms. The next slide (Table 4) consists of a tabulation of fever and parasitemia disappearance. It is seen that these three drugs all gave satisfactory results.

There were no immediate failures with hydroxychloroquine; there were 6 with propoquin (1.8 per cent) and there were 13 with chloroquine (4.3 per cent). Included in these chloroquine failures are two instances of death from anaphylactic reaction, apparantly due to the chloroquine injection. One of these was a child of 6 years who died following an injection of only 1.0 cc (40 mg of the base); the other was an adult who died immediately after a 3.0 cc (120 mg) injection. Neither of these patients had appeared gravely ill before the injection. Both developed severe urticaria, shortness of breath, marked apprehension, and then convulsions and death within a few minutes of the injection.

In our experience with propoquin, small doses of 90 to 150 mg for an adult have given excellent results with neither local nor systemic toxic manifestation. Hydroxychloroquine, both intramuscularly and intravenously, also gave excellent results without any evidence of toxicity, but our experience with this compound is more limited.

The number of known relapses is small. With chloroquin there were 8 among the 300 infections, all due to *P. vivax*, and all of which responded well to retreatment. With hydroxychloroquin there was one known relapse, and this patient responded to retreatment. Among 335 propoquin treated infections, there were 9 relapses, 7 in *P. vivax* cases, 2 in *P. falciparum* ones. Again, these all reacted favorably to retreatment.

TABLE 4 — *Immediate results of parenteral single dose treatment of malaria*

Adult dose [2] (Gm. of Base)	*P. falciparum* infections			*P. vivax* infections		
	Number of patients	Average number of hours until		Number of patients	Average number of hours until	
		Temp. remained normal	Parasites disappeared		Temp. remained normal	Parasites disappeared
Amodiaquin						
I. M. 0.15	10	—	—	—	—	—
Chloroquine						
I. M. 0.12 to 0.16	210 (10)[1]	29.8	34.1	90 (3)[1]	21.1	34.2
Hydroxychloroquine						
I. V. 0.36	26	24.3	21.5	—	—	—
I. M. 0.36	37	21.7	33.0	—	—	—
Propoquin						
I. M. 0.09 to 0.15	186 (4)[1]	22.2	30.0	149 (2)[1]	13.9	29.9

[1] The figure in parenthesis represents the number of patients in which the response to the single dose treatment was not satisfactory. These immediate failures to the single dose treatment are not included in the tabulation of the average number of hours until temperature remained normal nor the average number of hours for parasite clearance.

[2] Children under 12 years of age received proportionately less.

COMMENTS

I realize that, to stay within the allotted time, I have only barely outlined the results obtained in these three thousand and ten malaria infections. There are many questions remaining unanswered. I will touch on just a few, in the way of comment, and perhaps later discussion will bring out others.

It is well to emphasize, as we have previously done, that this study was done in an endemic malaria area where the adult indigenous population can be presumed to have developed a partial immunity. Obviously, results of treatment in a non-immune population or in an immune population of another location might be different. Also, variation in parasite strain in different localities might produce different responses.

As do many clinicians in many parts of the world, we routinely treat acute malaria attacks with a single dose of tablets or with a single injection. This is saving considerable time and money. Milder cases, which constitute the majority, remain ambulant. Patients who appear quite ill are usually hospitalized for one to three days, and these more severe ones are those who comprise the present study. Supportive and symptomatic therapy is frequently indicated, such as analgesics and intravenous fluids in vomiting patients, but further antimalarial treatment is invariably not indicated. Our routine oral treatment at the present time is with either amodiaquin or chloroquine, and our usual parenteral therapy is with intramuscular propoquin.

In this report, an evaluation of the incidence of radical cures effected by these antimalarials has not been attempted. Such an evaluation is never satisfactory in endemic malaria areas because immunity cannot be measured nor reinfection closely controlled.

SUMMARY

We have closely observed over 3,000 malaria infections treated with a single dose of an antimalarial drug, 2,302 of them with an oral medication, the remainder with an injection. The clinical observations included fever and parasitemia disappearance, toxicity, immediate treatment failures and relapses. As a result of these studies, our routine oral treatment at the present time is with either amodiaquin or chloroquine, and our usual parenteral therapy is with intramuscular propoquin.

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THE EFFECT OF MALARIA ERADICATION ON MORTALITY FROM NEPHRITIS IN BRITISH GUIANA

George Giglioli[1], M. D. (It.), M. R. C. P. (London),
D. T. M. & H. England

Wide discrepancies exist in the writings of different authorities concerning the incidence and significance of nephritis in the course of malaria infections.

Malaria, though substantially the same infection wherever it occurs, is subject to an extremely wide range of variation in its epidemiology in relation to environment: climate affects the relative incidence of the various parasite species and may influence the development of special strains; it regulates the season of transmission, its intensity and duration. Climate and other ecological factors thus directly affect the type incidence, severity and duration of malaria infections and the frequency of reinfections and super infections in the human population. In temperate climates malaria transmission is seasonal, *i. e.* periodically intermittent; in equatorial climates it is continuous throughout the year and the population gets no respite from the constant onslaught of reinfection. In civilized communities moreover the course of malaria attacks, however frequent, is usually interrupted by treatment at a more or less early stage; in backward or primitive countries, on the contrary, infection evolves uninterrupted, controlled only by the resistance and immunitary reactions of the patient. Under such widely varying conditions it is by no means surprising to find variations in the clinical manifestations of malaria and, more particularly, in the long term effects of these infections.

In temperate climates and in tropical areas subject to more or less mild or seasonal malaria, kidney involvement has been recorded in the course of infections with all three types of malaria parasites; the etiological relation between malaria and nephritis has, however, been accepted with reserve as the rarity of such cases made it difficult to exclude the accidental coexistence of the two conditions. Very careful studies on this subject were carried out by Rem Picci at the Santo Spirito Hospital in Rome from 1891 to 1898, at a time when close on fifty per cent of the cases admitted to that hospital were infected with malaria. Eighty cases were studied ranging from albuminuria to established chronic nephritis. The etiological relation with malaria was accepted and the importance of repeated attacks was stressed both as a primary cause of renal involvement and as an aggravating factor once kidney lesions had become established. Cases were more frequently associated with *P. vivax* and *P. malariæ* infections and children appeared to be more susceptible.

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[1] Medical Adviser — British Guiana Sugar Producers Association and Honorary Government Malariologist.

Thirty years later Paterni carried out further observations in the same hospital, from 1924 to 1928: he found a very substantial reduction in both the incidence and severity of renal symptoms in a series of 1470 malaria cases; he attributed this change to the greatly improved conditions of malaria control and treatment in the Roman Campagna.

Under tropical conditions, evidence of the etiological connection between malaria and nephritis has been much more abundant and specific; most observations have come from the equatorial belt where malaria transmission is continuous: Malcolm Watson in Malaya (1905), J. T. Clark in Malaya (1912), P. Manson Bahr and Maybury in cases originating from Malaya and India (1927), K. E. Surbek in Sumatra (1929, 1931, 1932), G. Giglioli in British Guiana (1930, 1932), W. G. Bosch in Java (1930), M. Wolsky and E. M. Schewelwa in Sumatra (1930), J. A. P. Lamberts Hille Ris in Surinam (1932), Y. C. Carrothers in Kavirondo, East Africa (1934), C. F. James in the Solomon Islands and New Guinea (1939), etc.

All these authors stress the preponderant, but not exclusive, importance of *P. malariæ* as the cause of chronic or subchronic nephritis, particularly in children, and young adults. These numerous and concordant observations confirm the conclusion we reached in 1930 that: «the conditions which favour malaria nephritis are not in the nature of contingencies bringing about a complication of a secondary or accidental character; they are conditions which influence directly and exclusively the epidemiological regime of malaria» (Giglioli, 1930).

According to Marchiafava and Bignani (1902), «any statement regarding the pathogenesis of renal lesions observed in malaria infections can only be given as an hypothesis: do we perhaps know by what process nephritis develops in scarlet fever? The knowledge of the specific organism which causes malaria, for the present at least, has thrown no light on the problem. In pernicious cases one finds only very few parasites in the vessels of the kidney; on the contrary, degenerative changes in the epithelial cells are serious and may go as far as actual nechrosis. From these findings one can conclude with Bignami that these lesions are not due to obstruction of the renal capillaries by the malaria parasites but to some toxic substance brought to the kidney by the blood stream for elimination. An increase in the toxicity of the urine would favour such a contention. As to the nature of the toxic substance capable of producing renal alterations nothing can be said. Are we in the presence of specific toxins elaborated by the malaria parasite or of toxic products resulting from the destruction of the parasite, the red blood corpuscles, the phagocytes or from the altered general metabolism? And, if toxins are always produced, why are renal complications rare? Which are the intermediary factors, which are capable of rendering the kidney susceptible to these toxins?»

Today most of these questions formulated over half a century ago, still remain unanswered; our new acquisitions concern the role of *P. malariæ,* the importance of long drawn out infections and reinfections and the lack or inadequacy of treatment. Owing to its mildness quartan fever tends to be neglected; it is also by a long way the most persistent and tenacious of the malaria infections; these characteristics might, therefore, account of themselves for the specific etiological role of this parasite in the production of renal disease apart from the existence of an hypothetical *P. malariæ* toxin.

In British Guiana, C. W. Daniels (1896) was the first to report the high incidence of nephritis; in a series of 926 autopsies performed in the Georgetown Public Hospital he found no less than 228 cases (24,6 per cent) with nephritis; with few exceptions the lesions were of a chronic nature. In the annual reports of the Registrar General of British Guiana Bright's Disease has consistently appeared as one of the most important causes of death with a high incidence among children and young adults; in the absence of any better designation, the term «endemic nephritis» was introduced.

In 1926 the Royal Society and the Royal Society of Tropical Medicine & Hygiene sent out a commission headed by A. W. Grace (1931) to investigate the bacteriological complications of filariasis and the endemic nephritis in British Guiana.

The commission spent two years in the colony concentrating its main effort on filariasis; studies on nephritis were limited to advanced cases admitted to the Georgetown Public Hospital, which caters prevalently for the Negro population of the city and larger villages. The important rural East Indian population of the sugar estates, which enjoys free medical assistance in the plantation hospitals, would thus be represented in the clinical material studied by the commission only by selected cases referred to the major institution either for surgery or for special treatment; the majority of East Indians which were studied were, in fact, described as vagrants belonging to the poorest class.

Overlooking the fact that Daniel's original observations were anatomical and not clinical, Grace took the view that the reported high incidence of nephritis in British Guiana was the result of considerable inflation by three factors: 1) the inclusion of cases of febrile albuminuria; 2) the tendency to record readmissions as new cases; 3) diagnostic errors mainly in relation to non renal dropsical conditions. The commission, accordingly, gave most of its attention to «epidemic dropsy», a condition neither clinically nor anatomically related to nephritis. This beri-beri-like disease, of doubtful etiology, would appear to have been remarkably common among destitute East Indians at the time; we have however had no similar experience during many years work both in the interior and on the sugar estates.

On 220 cases of confirmed nephritis, Grace classified 172 as parenchymatous and 48 as interstitial; out of 24 examined at autopsy one only had acute lesions; 7 had parenchymatous and 16 interstitial nephritis. Grace concluded: «It may be said with certainty that if any difference exists between the nephritis in British Guiana and that of temperate climates, this difference is one of etiology and is not to be found in the developed disease.» Such a conclusion is not surprising given the advanced stage of the cases studied and the exclusion of albuminuria associated with fever from the investigation.

In 1930 we published a monograph on malaria nephritis based on 7 years of continuous observation in the Demerara River district of British Guiana, an area in the interior subject to hyperendemic malaria:

102 cases were recorded; of these 37 were children under 16 years and 65 were adults, 9 only were over 45 years of age. Many cases were studied over a period of several years so that the progressive evolution of the disease was followed.

Nephritis occurred in all races; owing to the local constitution of the population, brought about by mining operations in the area, the majority of our patients were either Negroes or of mixed parentage; the disease however was most frequent among East Indians and in the autoctonous Amerindian or mixed riverine population which was particularly exposed to constant reinfection and had few facilities in respect to treatment.

Apart from confirmed clinical nephritis, albuminuria was very common: in a series of 9,510 physical examinations for employment, 4.6 per cent presented albuminuria, ranging in amount from a trace to 12 per mille. Among 70 miners whose urine was normal when examined at rest, 24.2 per cent developed albuminuria at the end of the day's work; in 15 per cent it persisted after 24 hours and became permanent as long as the work continued. Albuminuria was present in 25 per cent of cases with malaria parasites in their blood: in 25 per cent of *P. vivax*, in 20 per cent of *P. falciparum* and in 46 per cent of *P. malariæ* infections. Actual nephritis was observed in 48 per cent of patients with *P. malariæ* in their blood.

These studies were continued from 1933 to 1937 on three sugar estates situated on the Berbice River estuary and aggregating a population of approximately 4,000, mainly of East Indian race. The following table shows the relative incidence of albuminuria by age group among patients admitted to the hospitals of these estates.

Estate	Spleen rate	Percentage of patients with albuminuria					
		1-5 years	6-10 y.	11-15 y.	16-40 y.	Over 40 y	All ages
Blairmont	56	3,0	4,1	6,7	16,6	26,3	14,5
Providence	64	8,0	5,3	15,1	27,3	49,0	33,1
Bath	15	8,3	2,0	6,0	7,7	8,6	7,4

The great majority of the patients to which this table refers were infected with malaria. Many of the more elderly subjects were admitted for chronic, respiratory conditions; albuminuria was frequently present in such cases with only a few hyaline and granular casts in the sediment;

in due course more definite clinical signs of renal impairment made their appearance. We observed 25 cases of chronic nephritis in children from 2 to 16 years of age; malaria parasites were found in 10, all cases being *P. malariæ* infections.

In conclusion, all the data collected during 15 years of clinical work in the interior and on the coastal sugar estates confirmed the high incidence of Bright's disease in the rural population and its frequency in children and young adults, clearly incriminating malaria and *P. malariæ* infections in particular as the major cause of the so called «endemic nephritis» of British Guiana.

Between the years 1946 and 1951 malaria and its local carrier, *A. darlingi,* were eradicated from the coastlands and all permanently inhabited localities of the interior; this was achieved entirely and exclusively by spraying the interior of houses with DDT (Giglioli, 1948, 1951). Since 1953 one single autoctonous case of malaria has been recorded from the coastal area (West Demerara Water Conservancy, April 1955); a few cases are still reported each year from the far interior, but they are rare and all come either from the sparsely inhabited North-West district or from the frontier areas with the Rio Branco territory of Brazil, where, up to the present, no malaria control has been applied across the border.

It is now possible, six years from the successful conclusion of the malaria eradication campaign, to review the situation in respect to the incidence of nephritis, before and after eradication, as a final check of our findings of 1930 concerning the etiology of this very important local disease.

We have limited this investigation to the study of mortality statistics from the colony's sugar estates as such a limitation presents some advantages: the sugar estates are distributed throughout some two hundred miles of the territory's coastland and aggregate a population, mainly of East Indian race, of 95,200 (1957), equivalent to more than one quarter of the total rural population. Medical supervision on the estates, from the days of slavery and indentured immigration, has always been better than in the villages and towns, with free medical treatment at the estate dispensaries and hospitalisation facilities. On each estate birth and death registration records have been kept uninterruptedly; given the difficulties of rather primitive rural practice, diagnostic errors have undoubtedly been frequent, this however is less likely to have occurred in respect to fatal cases of a chronic and well characterised condition such as Bright's disease, particularly on the estates where patients are generally known personally to the dispensers and nurses. Finally by limiting this study to mortality returns the possibility of errors, due to the inclusion in statistics of repeat admissions to hospital as new cases, is entirely eliminated.

In the nineteen year period between 1939 and 1957 a total of 17,889 deaths were registered on the sugar estates; out of these, 1,622 were due to nephritis, either as the sole cause of death or in association with other conditions, usually malaria or chronic respiratory diseases. Acute nephritis was diagnosed only twenty seven times; the age group distribution of these cases is interesting:

One year or less	11 deaths
Two to five years	9 deaths
Six to ten years	2 deaths
Eleven years and over	5 deaths

It will be noted that the great majority of these cases concern infants and very young children; we have not been able to obtain any clinical information on these patients; particularly for the infants, the diagnosis should be accepted with great reserve and it is probable that none of the cases listed above are etiologically connected with the common subchronic or chronic disease with which we are concerned.

Table 1 presents for each year the number of deaths from all causes, the number of deaths attributed to malaria, those caused by chronic nephritis and, finally, the death rate from chronic nephritis per mille deaths registered; the estimated estate population for the years 1939, 1946, 1952 and 1957 is also given. We have not calculated the death rates per mille of population as reliable population figures are not available for each year and because some of the deaths registered in estate hospitals concern persons who do not reside on the estates; the latter situation repeats itself each year and does not therefore introduce an error of any significance in the general trend of mortality. The table is subdivided chronologically into three periods.

1939 to 1945: malaria endemic or hyperendemic throughout the estates.

1946 to 1951: DDT spraying campaign; malaria under progressively increasing control culminating in eradication.

1952 to 1957: malaria eradicated.

TABLE 1 — *Sugar estates of British Guiana: population, deaths from all causes and deaths from malaria and chronic nephritis from 1939 to 1957. The table is divided chronologically in three sections: before, during and after the malaria eradication campaign (1946-1951)*

	Year	Estate population	Deaths			
			All causes	Malaria	Chron. nephritis	
					Cases	Rate % deaths
	1939	67,000	1072	135	135	127
	1940	—	1017	86	115	113
	1941	—	867	63	106	122
	1942	—	1006	64	107	106
	1943	—	1489	149	150	100
	1944	—	1369	203	118	86
	1945	—	1036	144	104	100
Malaria eradication	1946	71,500	1020	108	119	117
	1947	—	913	51	103	113
	1948	—	883	34	96	108
	1949	—	871	27	68	79
	1950	—	971	8	88	92
	1951	—	864	4	64	74
	1952	83,650	913	2	58	64
	1953	—	818	0	42	52
	1954	—	729	0	40	55
	1955	—	769	0	30	39
	1956	—	641	0	28	44
	1957	95,200	641	0	15	23
	19 years	—	17,889	1078	1586	88.6

During the seven years which preceded the introduction of DDT, with an average estate population of 69,250, the deaths registered totalled 7,856 and of these 844 were caused by malaria and 835 by chronic nephritis. The death rate from nephritis, per thousand deaths registered, averaged 106, ranging from 86 in 1944 to 127 in 1939.

Throughout the malaria eradication campaign from 1946 to 1951, the estate population averaged 77,576; the deaths registered totalled 5,522; of these 232 were caused by malaria and 538 by nephritis. All figures show a substantial and progressive fall.

In the six years following the eradication of malaria the downward trend in death returns is even more evident: with an average estate population of 89,425 there were 4,511 deaths; of these 2 only were attributed to malaria; they occurred in 1952 and the diagnosis was not confirmed parasitologically.

Deaths from nephritis aggregated 213, falling progressively from 58 in 1952 to 25 in 1957 when estate population had reached the peak figure of 95,200.

The fall in the number of deaths from chronic nephritis since 1946 has been progressive but, as might be expected, much lower than the fall in deaths directly caused by malaria; it is thus likely that whereas the mortality from malaria reached zero in 1952, the mortality from nephritis may continue to maintain its downward trend during the next four or five years.

Table 2 analyzes all deaths registered under the diagnosis of nephritis, from 1939 to 1957, according to age group; for each year the average age of cases is also given.

During the seven years preceding the introduction of DDT, deaths from nephritis were numerous in all age groups; the average age of cases ranged from 38.3 to 47.5 years; out of a total of 836 deaths, 330, or close on 40 per cent, were under 40, and 136, or 16.2 per cent, were under 20 years of age.

During the DDT campaign years (1946 to 1951), the average age of cases dying from nephritis rose progressively from 44.8 in 1946 to 49.2 in 1950. Out of a total of 538 deaths caused by nephritis, 152, or 28.2 per cent, were under 40 and 46, or 8.5 per cent, were under 20 years of age.

In the six years period following the eradication of malaria, the average age of cases dying from nephritis further increased from 46.1 in 1952 to 56.3 in 1956. Out of a total of 213 deaths from nephritis, 30, or 14.1 per cent, were under 40, and only 13, or 6.1 per cent, were under 20 years of age. In 1957, finally, with an estate population of 95,200, there were only 15 deaths from nephritis and, of these, 2 only were under 40 and 1 single case was less than 20 years old.

Our diagram presents the various points which have been made in a more dramatic form. It should be noted, however, that the two periods considered, 1939 to 1946 and 1953 to 1957, are not equal and are thus not comparable quantitatively, the first covering 8 years and the second

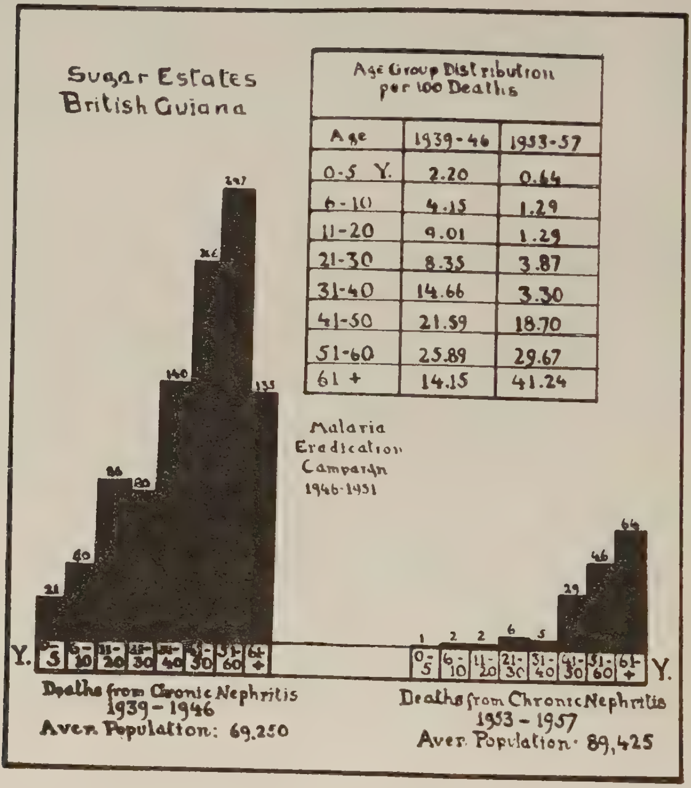
TABLE 2 — *Sugar Estates of British Guiana: Distribution by age group of deaths caused by chronic nephritis from 1939 to 1957. The table is divided chronologically in three sections: before, during and after the malaria eradication campaign. (1946-1951)*

	Year	Deaths from chronic nephritis									
		Deaths	Aver age	Distribution by age group							
				0-5	6-10	11-20	21-30	31-40	41-50	51-60	61 +
	1939	135	41.7	3	4	14	13	23	36	30	13
	1940	115	42.5	5	4	9	10	18	23	31	15
	1941	106	39.5	3	10	11	9	11	25	28	9
	1942	107	38.3	2	7	15	11	17	23	26	6
	1943	150	45.2	5	3	12	12	22	25	36	35
	1944	118	47.5	0	2	9	10	10	24	33	30
	1945	104	42.1	2	6	10	7	21	14	30	14
Malaria eradication	1946	119	44.8	1	4	6	8	18	36	33	13
	1947	103	48.2	1	2	6	6	15	23	29	21
	1948	96	47.5	1	2	6	6	16	18	33	14
	1949	68	47.4	1	1	5	5	8	14	18	16
	1950	88	49.2	1	2	2	4	11	21	22	25
	1951	64	48.2	1	2	2	4	5	18	20	12
	1952	58	46.1	3	3	2	4	2	14	19	11
	1953	42	53.7	0	1	1	1	2	9	11	17
	1954	40	55.2	0	0	1	1	1	8	15	14
	1955	30	56.2	1	0	0	3	0	2	11	13
	1956	28	56.3	0	0	0	1	1	6	7	13
	1957	15	56.0	0	1	0	0	1	4	2	7
	19 years	1,586	—	—	—	—	—	—	—	—	—

only 5. The age group distribution, in the inserted table, is however expressed as a ratio per thousand deaths registered so that figures are comparable.

These studies confirm our clinical and epidemiological findings of thirty years ago incriminating malaria as the principal cause of what was then called «the endemic nephritis of British Guiana». They also indicate how wide and pernicious is the effect of severe endemic malaria and how far it extends beyond the obvious damage as expressed by direct malaria mortality and morbidity returns. We have illustrated elsewhere how the eradication of malaria has affected the incidence of megalocytic anaemia of pregnancy, a common nutritional disease amongst

East Indian women in British Guiana; maternal, foetal and neonatal mortalities have been drastically reduced. We now find that on the sugar estates of British Guiana, during the 19 years period considered, Bright's disease actually caused more deaths than malaria itself, yet the cause of these two diseases, apparently so different, was undoubtedly one and the same. It is through such apparent «by effects» that malaria



Age Group Distribution per 100 Deaths

Age	1939-46	1953-57
0-5 Y.	2.20	0.64
6-10	4.15	1.29
11-20	9.01	1.29
21-30	8.35	3.87
31-40	14.66	3.30
41-50	21.59	18.70
51-60	25.89	29.67
61 +	14.15	41.24

Sugar estates of British Guiana diagramatic representation of age group distribution of deaths caused by chronic nephritis before and after the malaria eradication campaign (1946-1951). The two diagrams are not comparable quantitively as the pre-eradication period (1939-1946) comprises eight years while the post-eradication period (1953 to 1957) comprises only five years. The figures in the inserted table are however comparable as they refer to age group mortalities for every one hundred deaths caused by chronic nephritis during the two periods.

eradication brings about its widest benefits; thus in British Guiana it has caused the crude vital index to soar, in only 12 years, from 130 in 1944 to 387 in 1956.

SUMMARY

Chronic nephritis was a common disease and one of the major causes of death, in all age groups, in the population of the highly malarial rural areas of British Guiana; in some years it caused more deaths than malaria itself. The present paper analyzes the mortality from nephritis on the sugar estates of British Guiana from 1939 to 1957. In a population which during this period averaged 81,000, 17,889 deaths were registered; of these, 1,078 were directly attributed to malaria and 1,587 to chronic nephritis. Malaria was eradicated between 1946 and 1951; no parasitologically confirmed death has been registered since 1952 and only one autoctonous clinical case was recorded in April 1955. The number of deaths from Bright's disease has shown a steep and progressive fall in parallel with the decline and final eradication of malaria; chronic nephritis has become a rare condition in children and young adults. The specific role of malaria in the etiology of the so called «endemic nephritis of British Guiana», as sustained by the writer in 1930, on clinical and epidemiological grounds, is thus confirmed.

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FURTHER STUDIES ON CHLOROQUINIZED TABLE SALT[1]

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The mass suppression of malaria by the use of sodium chloride mixed with proper amount of a suitable antimalaria drug was first tested by Pinotti and his co-workers (Pinotti, 1953; Pinotti *et al.*, 1955; Pinotti & Soarez, 1956), and has been proved to be an efficient means of control whenever the DDT fails. Beside the field tests, laboratory studies have demonstrated that the chloroquine possesses sufficient chemical stability to resist usual cooking conditions without significant decomposition (Paulini, 1953). These results have been confirmed and also extended to the pyrimethamin by Coatney and co-workers (1958).

The studies on the concentration of the chloroquine in the blood, using different daily doses, and the elimination by the urine and possibly through the human milk (Paulini, Soares, Pereira, 1957); (Soares, Paulini, Pereira, 1957) have completed preliminary studies. During these investigations some new analytical techniques have been developed for the determination of the chloroquine either in the salt or in different body fluids (Paulini, 1953, 1954, 1955; Pereira & Paulini, 1956).

In September, 1956 the first regular large-scale application of the chloroquinized salt has begun in Engenheiro Dolabella County in the State of Minas Gerais, protecting about 8000 persons. This was followed by a project in the State of Santa Catarina, having been started at the end of 1957, and another in the Federal Territory of Amapá, which was begun in the first months of this year. The two latter projects will cover an area of 140 000 km² with an estimated population of 65 000.

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[1] Apresentado aos VI Congressos Internacionais de Medicina Tropical e Paludismo, Lisboa, Portugal, 3-11 de Setembro de 1958, Divisão B, Secção 4. Trabalho do Departamento Nacional de Endemias Rurais (Director-Geral: Dr. Mário Pinotti).

The large-scale application of Pinotti's method has brought up several problems hitherto not considered, such as:

a) A simple, but efficient process for the preparation of chloroquinized salt;
b) Field techniques for the control of the distribution of the salt among the population;
c) Laboratory technique for the control of ingestion of the salt;
d) The keeping quality of the chloroquinized salt during prolonged storing under humid conditions;
e) The concomitant use of iodate and chloroquine in the salt.

In the following a brief account will be given of the work done on these problems, but it is stressed that still more time and study is needed until the most satisfactory solutions will be found.

1. *Preparation of chloroquinized salt*

Two processes are actually used in Brazil; one of them is essentially manual, intended for supplying small areas up to 10 000 habitants, while the second process uses a mechanical mixer, having a production capacity of up to 2 m. t. per day.

Process 1

Weigh 60 kg of salt and pass it through a coarse sieve of 8 mesh; break up any lumps found. Add 700 ml of chloroquine diphosphate solution (prepared by dissolving 600 g of chloroquine diphosphate in one and half (1-½) liter of clean water, then brough up to 2100 ml) distributing it evenly over the salt, then mix by shoveling for 10 minutes. Pass the mixture through the sieve again and fill in sacks.

Process 2

First prepare a salt concentrate by mixing 56 kg of salt and 4 kg of chloroquine diphosphate. Care should be taken that the drug is added slowly and evenly — preferably through a fine mesh sieve — to the bulk of the salt, which should be continuously revolved during the addition of the drug. When these precautions were not observed the moist salt caused the drug to form small, ball-like aggregates which could not be desintegrated later on and the final mixture became inhomogenous. The homogenization of the salt concentrate is best done in the mechanical mixer. Take 6 kg of the salt concentrate, place into mixter and under continuous rotation and slowly 114 kg of salt. Mix for another 5 minutes, then discharge. (Total mixing time about 10 minutes.)

Samples of salt produced by both processes were analysed regularly at bi-weekly intervals and their concentration of chloroquine as diphosphate was within the limits of 0.33 % ± 0.03 %.

2. *Control techniques*

The distribution of the chloroquinized salt among the population is controlled by house to house visits, testing the salt for chloroquine by the following process:

a) 1 to 2 grams of salt is placed in a clean test tube and about 5 ml of clean water is added. It is not necessary to dissolve the salt completely.

b) Mix the content of the test tube by agitating it then add 2-4 drops of a 1 % iodine solution. In the presence of chloroquine a dark, reddish brown precipitate is formed; in its absence the solution turns only to pale yellow.

The ingestion of the chloroquinized salt is tested only in persons who were found with malaria in the areas under control. Urine was collected from these persons; it was preserved with the addition of salicilic acid and sent to our laboratory for quantitative analysis. The results (Table 1-*a*) indicate that only in two instances have small elimi-

TABLE 1-*a* — *Apparent chloroquine concentration in the urine of persons who did not regularly use chloroquinized salt*

Initials	V. B.	M. N. S.	M. F. G.	M. R.	A. G.	M. A. G.	J. M. L.
mg of chloroquine per 100 ml of urine	0,16	0,07	0,14	0,18	0,19	0,34	0,36

nations of chloroquine been found in the urine, indicating irregular intake of the drug, whereas the remainder probably had not taken the drug for at least 15 days preceeding the date of the sampling. For comparison see Table 1-*b*, showing normal rate of elimination.

TABLE 1-*b* — *Apparent chloroquine concentration in the urine of persons taking regularly daily doses of 20 mg of base*

Number of days after medication started	0	3	7	14	20	26	32
mg of chloroquine per 100 ml of urine	0,04	0,09	0,16	0,39	0,40	0,53	0,68

3. *Keeping quality of the salt under humid conditions*

The first observations on the rapid loss of chloroquine under extreme humid conditions were made in our laboratory in 1954, but investigation of this problem has only been started early this year. Common, ground salt, containing 1.4 % *Ca* and 0.6 % *Mg*, was mixed with chloroquine diphosphate by both processes given previously and distributed in small cotton bags, each containing about 300 grams of product. These bags were suspended in constant humidity chambers, where the atmosphere was maintained at RH 100 % by keeping dishes with water on the bottom of the chamber. At 15-day intervals one bag was removed from each group of samples and analyzed, layer by layer, for chloroquine.

Already after the first 15 days a significant drop has been observed in the concentration of the chloroquine in the top layer of the salt, but not in the center, nor in the bottom layers. The water content of the salt rose from an initial 0.5 % to 6 %. The bags have received a humid aspect and drops of liquid were forming on their bottom.

In the following 30 days the drug was almost completely lost from the superficial layers and only a fraction of the original concentration remained in the central part of the bag and in the bottom layer. The water content of the salt did not increase above 7 %.

The leaching process by which the chloroquine is lost can be reconstructed as follows: the calcium and magnesium compounds found in the common salt increase the water content of the salt by absorbing water vapor from the atmosphere when the relative humidity is high. When the water content of the salt has attained its critical value (about 6 %) the liquid phase starts to move downwards following the gravity gradient and carries away the chloroquine in dissolved form. The concentrated salt and chloroquine solution is absorbed by the textil material of the bag. It seems that the penetration of the liquid or humidity into the center of the bags is a much slower process and the migration of drug from this part is more delayed. This may explain that the change in concentration of the drug has never interfered with the good results obtained in the field.

Samples of salt kept under humid conditions in the field have shown a decrease of the drug concentration in the top layer (see Table 2), whereas samples taken from bags stored under dry conditions (RH less than 80 %) did not show significant modification in the drug concentration and distribution in the salt during the first four months, which was during the dry season, but only after the onset of the rainy weather (see Table 3).

TABLE 2 — *Chloroquine concentration in bags stored under humid conditions in the field. — Sample taken from the top layer*

Days after preparations	Bag n.° 1 (%)	Bag n.° 2 (%)
0	0,33	0,34
7	0,29	0,28
14	0,21	0,19
35	0,12	0,15
45	0,17	0,04

TABLE 3 — *Chloroquine concentration in a bag stored under dry conditions in the field. — Sample taken from the top layer*

Months after preparation	0	1	2	3	4	5	6
Chloroquine diphosphate %	0,33	0,32	0,34	0,34	0,36	0,20	0,28

4. *Concomitant use of iodate and chloroquine in the salt*

Since January 1957 the salt destined for human consumption in Brazil should be mixed with potassium iodate, at the rate of at least 17 mg/kg, according to recent governmental regulation.

Preliminary laboratory experiments did not reveal any significant reaction between chloroquine and iodate in water solution when it was kept boiling for several hours. Nevertheless, in the field the first batches of chloroquinized salt prepared with iodized salt have developed a strong «drug» smell after about 4 weeks and the population refused to accept this product. Analysis of this salt showed only traces of iodate instead of the original 18 mg/kg. Further studies also showed that part of the iodate was reduced to free iodine, which in turn produced iodoform after reacting with the chloroquine. The reaction was apparently more rapid in acid or neutral media and slower in the presence of buffering agents like calcium carbonate or magnesium oxide (see Table 4). Since iodide did not react with chloroquine, it was decided, as a temporary measure, to add sodium thiosulphate as a reducing agent to the iodized salt. Under such conditions the iodate is reduced to iodide and the reaction with chloroquine is prevented.

TABLE 4 — *Decomposition of iodate in the presence of chloroquine*

Stabilizer	Time of reaction in hours	*pH*	% of decomposition of iodate at the end of reaction
None	12	3.5	54
None	12	3.9	35
None	12	5.3	14
None	12	6.9	12
Starch	15	3.7	35
Starch	15	5.5	30
Starch	15	7.0	30
$CaCO_3$	33	7.2	13
MgO	33	9.1	14

In actual practice, 15 gr of crystalline sodium thiosulphate dissolved in 100 ml of water is added to each 60 kg of salt before the mixing with chloroquine.

As mentioned previously, this measure is considered a temporary one and the definite solution of this problem would in our opinion be the preparation of a stabilized mixture of chloroquine and potassium iodide which, added to the crude salt, might remain unchanged for several months and could efficiently control both malaria and endemic goiter. Experiments to this effect are under way in our laboratory.

CONCLUSIONS

1 — Chloroquinization of the salt may be done either manually or mechanically, by simple processes;

2 — Distribution of the chloroquinized salt among the population can be checked periodically through house to house visits, using the iodine test for chloroquine;

3 — Urine samples may be taken and analyzed for chloroquine in order to check the ingestion of the salt;

4 — The chloroquinized salt prepared by the processes indicated above had good keeping quality in regions of low relative humidity (less than 80 %), but under humid conditions (RH above 80 %) leaching of the drug was observed with gradual loss of uniformity.

5 — Iodate and chloroquine should not be used in the same salt, unless care is taken to prevent any posterior reaction between the two; this can be done, for example, by adding sodium thiosulphate.

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THE INFECTIVITY OF THE PATIENT TO MOSQUITOES IN THE EARLY STAGES OF PRIMARY *VIVAX* MALARIA (MADAGASCAR STRAIN) COMPARED WITH RELAPSES

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On examining our records over the past thirty-five years we found that much information had been accumulated about the infectivity of patients in the developed stage of the primary attack of ***P. vivax***, but none about their infectivity during the first few days. Neither had we any information concerning the infectivity of patients to mosquitoes during the asymptomatic period of a relapse.

Irrespective of the number of sporozoites injected into a non-immune patient, gametocytes are seldom present in sufficient numbers to be detected easily in the peripheral blood until about the sixth or seventh day of parasitaemia. From their appearance on abut the seventh day of an untreated primary attack, the male gametocytes increase in numbers daily until about the twelfth day. From about the fourteenth day onwards, they decrease and often disappear altogether a few days later, especially if, as often happens, the attack ends in spontaneous recovery. In our investigations into the infectivity of patients in the early stages of a primary infection, we employed the following method:

Fifty-four patients were infected by the bites of mosquitoes. Four thick and thin blood films were taken once daily from each patient beginning on the seventh day after infection. On the first day of fever, or when a parasite was first found, whichever occurred first, one hundred laboratory bred mosquitoes were fed on the patient and this procedure was carried out daily until suppressive or curative therapy was administered. The fed mosquitoes were incubated at 27° C and were dissected and examined for oocysts on the seventh day after feeding. By feeding one hundred mosquitoes daily we were assured of having at least forty alive to dissect on the seventh day. The quantity of blood taken up by forty mosquitoes is considerably more than can be examined for gametocytes by two workers in a reasonable time, even with thick films. This probably explains why occasionally one mosquito out of forty may be infected with a single oocyst when no male gametocytes could be found after a prolonged search of a thick film.

The fifty-four patients may be summarised as follows:

1. The incubation period varied between eight and eighteen days.
2. The prepatent period varied between nine and eighteen days.
3. The earliest day on which male gametocytes were found varied from fifteen to twenty-one days after infection.
4. The earliest day of patients becoming infective to mosquitoes varied from the thirteenth to the twentieth day.
5. Mosquitoes which became positive on the first day of infectivity varied from five to one hundred per cent.
6. The number of oocysts per gut varied from one to fifty.
7. In only five of the fifty-four patients did we find parasites one or two days before the onset of fever.
8. From thirty-two patients, mosquitoes became infected before gametocytes were found. From twenty-two patients, mosquitoes became infected on the first day of finding a male gametocyte.

The shortest incubation period was eight days and this was seen in five of the fifty-four patients. This, we believe, probably represents the shortest possible incubation period for *P. vivax* and suggests that at least some of the pre-erythrocytic parasites completed their development in six days.

Several patients infected mosquitoes even when no male or female gametocytes could be found after a prolonged search of thick and thin films.

An interesting feature of this investigation is that in most of these patients, the longer the pre-patent period the earlier the mosquitoes became infected. In only one patient was the pre-patent period as long as eighteen days and mosquitoes which fed on him on the second day became infected. He was also the only patient in the series who had had malaria before in world war 2.

The relapses studied in this series were those occurring in patients who showed renewed parasitic and clinical activity within eight weeks of recovery from the primary attack which had been terminated by antimalarial drugs. In a relapse, parasites are nearly always demonstrable in a thin film on the first day of a clinical attack and gametocytes are usually present in proportionate numbers at that time. This is in contrast to what occurs during the same period of the primary attack. The explanation is obvious. In the primary attack, because of the absence of immunity, premunition or tolerance, very few parasites are necessary to cause fever. In a relapse there is some degree of tolerance as the result of the primary attack and therefore many more parasites are necessary to produce the same effect. In other words, in relapses parasites are present in the peripheral circulation several days before the onset of fever. This explains why gametocytes are often present in large numbers on the first day of clinical symptoms in a relapse.

Although the series is a small one, consisting of only eleven patients, all had fever and parasitaemia covering a period of ten to fourteen days and in our experience this is sufficient to enable a patient to develop some degree of tolerance but not immunity. All the patients were under continuous observation from the termination of the primary attack until relapses occurred.

In all cases thick and thin films were examined daily beginning on the seventh day after the completion of treatment of the primary attack. On the first day of parasitaemia, fifty mosquitoes were fed and this was repeated daily until antimalarial drugs were given or until there was a spontaneous recovery. The technique employed was the same as that used for the enquiry into the primary infection, except that only twenty mosquitoes were dissected and examined for oocysts in each patient. Mosquitoes failed to become infected when fed on the first or second day of parasitaemia. This applied to every one of the eleven patients. On the other hand, every patient was infective to mosquitoes when fed on the first day of fever.

Parasites were found in ten of these eleven patients three to six days before the onset of fever. Gametocytes were found in all cases by the third day of parasitaemia and mosquitoes which were fed at this time became infected. To quote one example:

We were able to observe a patient over a period of several months. Parasites were found six days before the onset of fever. From the third day of parasitaemia and for the next twenty-four days, a batch of mosquitoes was fed on him daily and was invariably positive. After three peaks of fever he developed a spontaneous recovery but continued to be infective to mosquitoes for a further eighteen days. Because the patient became very anaemic he was given antimalarial drugs but a month later parasites were again detected in the peripheral blood and on the fifth and sixth day of parasitaemia mosquitoes fed on him became infected. No fever occurred, no antimalarial drugs were given and a few days later parasites could no longer be found.

Our studies have shown that there are fundamental differences between the first few days of a primary attack compared with the corresponding period of a relapse, even in the same patient. In the primary attack the patient feels ill as soon as his peripheral blood is invaded by parasites. He will seek medical advice and providing malaria is diagnosed, appropriate treatment will in most cases sterilise the blood before gametocytes have developed. This is in contrast with relapses.

As our observations show, most of the patients who relapsed had demonstrable parasitaemia for several days before fever began and none of them complained of feeling unwell during this pre-clinical period. The fact that all of them were infective to mosquitoes before clinical symptoms developed is, we believe, of considerable epidemiological importance, especially when, as sometimes happened, one hundred per cent of the mosquitoes which fed on the patients became infected during the pre-clinical period.

We should have liked to repeat these observations with *P. falciparum*. Unfortunately, this is not possible because this species of parasite is no longer maintained in our laboratory.

As we have stated in a previous paper, our investigations indicate that a wide margin of error may occur during malaria surveys if infectivity to mosquitoes is estimated by the examination of blood films. There is a limit to the length of time that can be devoted to the examination of a blood film, especially under the conditions prevailing in field surveys. Our findings show that even after a prolonged search for gametocytes with negative results, a small percentage of mosquitoes become infected. This is especially applicable in the early days of a primary attack and in the post febrile stages of relapses.

OBSERVATIONS ON PRIMAQUINE IN THE PROPHYLAXIS AND CURE OF *VIVAX* MALARIA[1]

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Flanagan, Paul E. Carson, Stanley L. Schrier,
Robert W. Kellermeyer and Alvin R. Tarlov

Impressive evidence suggests that the 8-aminoquinoline drug, primaquine, is more active against the primary tissue schizonts, or pre-erythrocytic forms of *Plasmodium vivax,* than against the secondary tissue schizonts, the persisting exoerythrocytic forms to which relapses have been attributed. Patency can be completely prevented in intense, experimental Chesson strain infections by daily administration of primaquine, begun the day before induction of infection by mosquitoes and continued for seven subsequent days (1). An identical therapeutic regimen, begun after patency, is almost completely ineffective in preventing relapses if it is terminated after only seven days, even though chloroquine, which potentiates the curative action of primaquine (2), is given concomitantly for the management of the acute attacks (3). Judged only on its intrinsic aintimalarial properties, primaquine, therefore, should be more valuable in the prophylaxis of *vivax* infections than in their cure; yet it has been used almost exclusively for the radical cure of autochtonous *vivax* malaria, in which it has proved very effective in most areas when administered daily for two weeks.

The necessity for daily administration of primaquine constitutes a major limitation to its use. Moreover, if the recommended daily dose of 15 mgm base is exceeded, severe, acute hemolytic anemia is precipitated in approximately ten per cent of American negroes and various proportions of many other racial and ethnic groups in widely separated areas of the world, due to a genetically transmitted enzymic deficiency (glucose-6-phosphate dehydrogenase) in their erythrocytes (4). The incidence of this genetic abnormality is high in Southern Italians (5), Sephardic Jews (6) [1].

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[1] From the University of Chicago-Army Medical Research Project. This investigation was supported (in major part) under Contract Number DA-49-007--MD-566 between the Office of the Surgeon General, United States Army, and the Department of Medicine of the University of Chicago. Additional support was obtained from the Douglas Smith Foundation, The University of Chicago, Chicago 37, Illinois, U. S. A.

Doses in excess of 15 mgm base daily are required for the radical cure of *vivax* malaria acquired in some islands of the Southwest Pacific, particularly those in the New Guinea area. The comparative challenge of the Chesson, St. Elizabeth, and three Malayan strains of *vivax* to radical cure by daily administration of primaquine is illustrated in Fig. 1. The daily dose of primaquine that causes radical cure in all Malayan infections is only 60 % effective against the Chesson Southwest Pacific malaria, which requires higher doses of 8-aminoquinolines for radical cure than any other strain of *vivax* which we have studied experimentally. This figure also demonstrates the lack of relationship between the severity of challenge to radical cure by primaquine and the natural pattern of clinical activity if each attack is treated with quinine (8, 9).

We wish to present the progress of current investigations which explore the effectiveness of weekly primaquine administration, particularly its potential value in the prophylaxis of *vivax* malaria, with the aim of expanding the usefulness of this important antimalarial drug.

Our basic studies were designed to answer the question: Are the sporozoites and all primary tissue schizonts of *Plasmodium vivax* equally susceptible to the antimalarial action of primaquine? Non-immune, adult, male inmates at Stateville Penitentiary, who were known to be non-sensitive to the hemolytic action of primaquine, served as experimental volunteers [2]. A single large dose of primaquine, was administered to each man either before or after inoculation with Chesson *vivax* by ten heavily infected *Anopheles quadrimaculatus* mosquitoes (8). Untreated control and experimental subjects were bitten in groups by the same mosquitoes.

Only one of nine subjects (Fig. 2) who received a single dose of 120 or 180 mgm of primaquine base, either 4 or 12 hours before infection

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[1] Unfortunately, however, many other drugs, some of them in common use, also cause hemolysis in persons whose erythrocytes exhibit the genetic defect (4, 5, 6, 10).

[2] Primaquine was administered in the form of the diphosphate salt (56.9 per cent base).

HEAVY EXPERIMENTAL INFECTIONS OF VIVAX MALARIA	NATURAL PATTERN OF CLINICAL ACTIVITY	CHALLENGE TO RADICAL CURE
		PRIMAQUINE[1] Effectiveness of 15 mg. base daily
MALAYAN		
TAIPING Strain	CHESSON Type	100 %
PAHANG Strain	CHESSON Type	100 %
KEPONG Strain	CHESSON or ST. ELIZ. Type	100 %
SOUTHWEST PACIFIC CHESSON Strain	SHORT LATENCY After Primary 2 - 4 Weeks	60 %
ST. ELIZABETH Strain	LONG LATENCY After Primary 10 - 14 Months	Estimated 100 %

Fig. 1

by mosquitoes, developed parasitemia, and he experienced the unusually long prepatent period of 95 days. In contrast, 180 mgm administered either 24 hours before, or on the third, fifth or seventh day after infection, failed to prolong patency significantly in 14 out of 17 volunteers. The duration of the prepatent periods in untreated controls was 14 days or less. These results allow us to conclude that the earliest forms of primary tissue schizonts (cryptozoites), and possibly the sporozoites, are more susceptible to the antimalarial action of primaquine than are the intermediate or late mature primary tissue forms (metacryptozoites). The effectiveness of the single dose given 12 hours before infection suggests, but does not prove, that the sporozoites are vulnerable to primaquine or to one of its degradation products.

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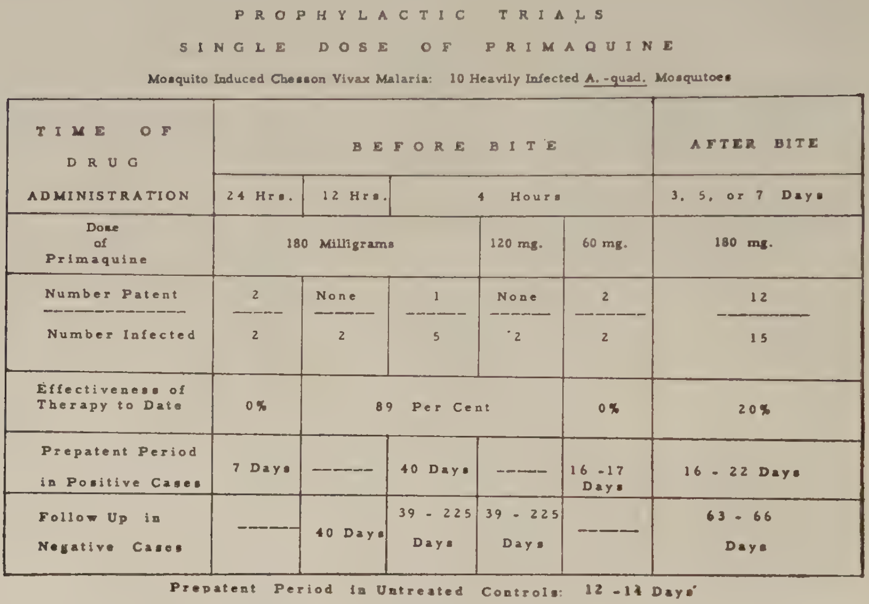
[1] With concurrent quinine or chloroquine.



PROPHYLACTIC TRIALS

SINGLE DOSE OF PRIMAQUINE

Mosquito Induced Chesson Vivax Malaria: 10 Heavily Infected A. -quad. Mosquitoes

TIME OF DRUG ADMINISTRATION	BEFORE BITE					AFTER BITE
	24 Hrs.	12 Hrs.	4 Hours			3, 5, or 7 Days
Dose of Primaquine	180 Milligrams			120 mg.	60 mg.	180 mg.
Number Patent / Number Infected	2 / 2	None / 2	1 / 5	None / 2	2 / 2	12 / 15
Effectiveness of Therapy to Date	0%	89 Per Cent			0%	20%
Prepatent Period in Positive Cases	7 Days	------	40 Days	------	16 -17 Days	16 - 22 Days
Follow Up in Negative Cases	------	40 Days	39 - 225 Days	39 - 225 Days	------	63 - 66 Days

Prepatent Period in Untreated Controls: 12 -14 Days

Fig. 2

These results pose a second question of both theoretical and practical importance: Can the danger of acute intravascular hemolysis in primaquine-sensitive individuals be prevented by weekly administration of the drug? Healthy, adult volunteers, who had recovered from severe, drug-induced hemolytic reactions several months previously served as experimental volunteers. The composite findings in three primaquine-sensitive subjects are presented in Fig. 3. The intravascular crises precipitated by the daily administration of 30 mgm of primaquine base were characterized by an acute fall in the hemoglobin and hematocrit, marked reticulocytosis and subsequent recovery (upper half of Fig. 3). While this acute hemolytic anemia is self-limited because the younger cells are more resistant to hemolysis by the drug than are the older cells, it nevertheless represents a very dangerous reaction, especially if it occurs during a malarial paroxysm when the urine output may be reduced.

Only slight hemolysis, no greater than that commonly observed in primaquine-sensitive individuals during the daily administration of the therapeutically safe dose of 15 mgm base, and detectable increase in reticulocytes, occurred after the weekly ingestion of 60 mgm of primaquine for 8 weeks (lower half of Fig. 3). It is, therefore, concluded that 60 mgm of primaquine base may be administered with safety on a weekly schedule for at least two months to adults, but this weekly dose should not be exceeded without medical supervision.

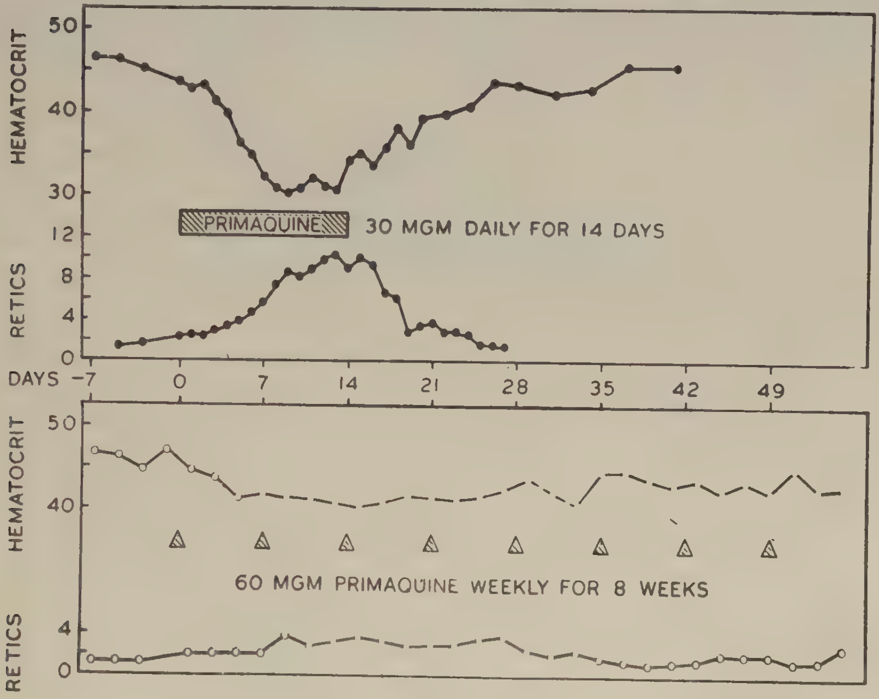
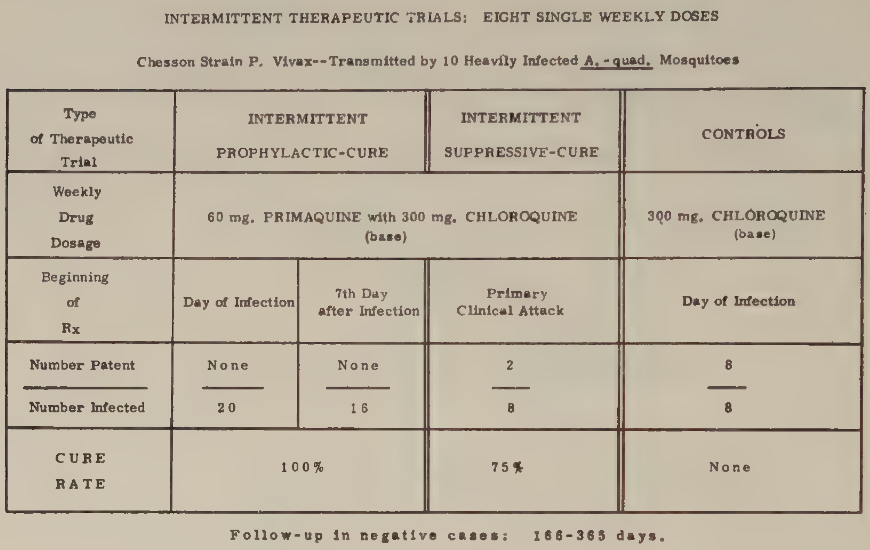


Fig. 3

The final question follows logically: Can prophylaxis or radical cure of severe *vivax* infections be achieved by weekly administration of 60 mgm of primaquine base combined with a quick-acting schizontocide? The results in heavy experimental Chesson *vivax* infections are presented in Fig. 4. In *prophylactic trials,* none of 36 volunteers who were started on the combined weekly administration of primaquine and chloroquine on the day of infection by mosquitoes developed parasitemia or fever during the follow up period of 166 to 365 days. The results in *curative trials,* though somewhat less impressive, are still good. Only two of eight volunteers in whom the regimen of weekly therapy was started during the primary clinical attack have relapsed.



INTERMITTENT THERAPEUTIC TRIALS: EIGHT SINGLE WEEKLY DOSES

Chesson Strain P. Vivax--Transmitted by 10 Heavily Infected A. - quad. Mosquitoes

Type of Therapeutic Trial	INTERMITTENT PROPHYLACTIC-CURE		INTERMITTENT SUPPRESSIVE-CURE	CONTROLS
Weekly Drug Dosage	60 mg. PRIMAQUINE with 300 mg. CHLOROQUINE (base)			300 mg. CHLOROQUINE (base)
Beginning of Rx	Day of Infection	7th Day after Infection	Primary Clinical Attack	Day of Infection
Number Patent / Number Infected	None / 20	None / 16	2 / 8	8 / 8
CURE RATE	100%		75%	None

Follow-up in negative cases: 166-365 days.

Fig. 4

We conclude that the prophylaxis and, probably, cure of natural acquired *vivax* infections may be achieved by weekly administration of primaquine in doses that are safe when combined with the standard suppressive dose of a 4-aminoquinoline (chloroquine, amodiaquine or hydroxychloroquine). For most infections, a weekly dose of 45 mgm of primaquine base would probably be effective because experimental infections studied by us were very heavy.

These investigations must be expanded and at least three additional questions should be answered before the weekly regimen can be translated into unsupervised use. What is the minimum time necessary for the prophylaxis or cure by intermittent combined drug administration in severe Chesson infections? What dose of primaquine may be administered safely on a weekly basis to primaquine-sensitive infants and children? What toxicity, if any, would result from the prolonged administration of these drugs?

The obvious advantage of the weekly over the daily schedule of primaquine administration may eventually lead to its freer use in endemic areas as an ancillary weapon in the final eradication of residual malaria after intensive use of insecticides or, in limited areas, as a substitute for their use after resistance of mosquitoes to insecticides has developed; but the greatest value of the weekly therapeutic regimen will probably be in routine treatment of people returning from malarious areas, thereby countering the reintroduction of the disease into an area where there is «Anophelism without malaria».

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RAISED GAMMA-GLOBULIN IN GAMBIAN AFRICANS: ITS RELATION TO MALARIA. A PRELIMINARY COMMUNICATION

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To assess the effects of repeated heavy erythrocytic infection in African infants and young children an investigation in a hyperendemic malarial district of the Gambia began in 1951. Among the results obtained it was found that malarious children developed significantly higher gamma-globulin levels than children from the same environment protected from birth by continuous chemoprophylaxis. (McGregor *et al.*, 1956). Subsequent examination of sera from symptom-free adult Gambian men and women from the same area showed gamma-globulin levels similar to those found in the malarious children (McGregor and Gilles, *loc. cit.*). A series of investigations designed to elucidate the etiological significance of these findings was begun in 1954.

All the subjects were drawn from the Sukuta area of the Gambia where malaria is hyperendemic. Members of the experimental groups were visited weekly by a European nursing sister, who administered chloroquine (6 mg of base per kg) or pyrimethamine (12.5 mgms) to the protected and a placebo to the unprotected series. All the subjects were admitted annually to the M. R. C. research ward for detailed investigation which included a clinical, nutritional, parasitological and haemotological assessment. Total serum protein was estimated by the micro-Kejdal method. Protein fractionation was carried out by filter paper electrophoresis and gamma-globulin expressed as a percentage of the total protein.

I. *Gamma-globulin levels of new-born Gambian infants (cord blood).*

The mean gamma-globulin value in 10 cases examined was 20.0 % (S. D. 3.22).

COMMENT

These results are very similar to those obtained by Stanier and Thompson (1954: 20.1 %) in a hyperendemic malarious area of Uganda, and higher than those reported from America and Europe. (Longsworth *et al.*, 1954: 15.7 %, Josephson and Gillensward, 1957: 14.6 %).

II. *The evolution of gamma-globulin in the first nine months of life in Gambian infants protected from malaria from birth by continuous chemoprophylaxis (Slide I).*

The mean levels for gamma-globulin concentration in each three-month age group are shown in Table 1, together with the results for unprotected Kampala African infants and white American infants.

It will be noted that, firstly, the drop in gamma-globulin concentration that occurs between the second and sixth months of life is not

TABLE 1 — *Mean serum gamma-globulin values of African (Gambian and Uganda) infants and of white American infants in the first month of life and at successive trimesters*

Subjects	No.	Age in months	Gamma-globulin (%)	Standard deviation
Chloroquine	6	1st Month	19.5	3.13
Protected Gambian	8	1-3 M.	14.1	3.08
Infants	11	3-6 M.	17.0	3.00
	4	6-9 M.	17.0	2.32
Pyrimethamine	9	1st Month	20.0	3.31
Protected Gambian	6	1-3 M.	14.7	1.77
Infants	6	3-6 M.	13.0	1.59
	9	6-9 M.	16.1	1.95
White American	18	1st Month	15.8	4.48
Infants	7	1-3 M.	7.4	1.98
(Moore 1949)	3	3-6 M.	6.4	1.84
Uganda Infants	20	1st Month	21.5	4.7
Unprotected	20	1-3 M.	13.5	4.1
(Thompson 1956)	20	3-6 M.	14.1	5.1
	20	6-9 M.	16.7	7.0

so marked as that which occurs in American infants. Secondly, by the ninth month the gamma-globulin levels obtained (16.1 % — 17.0 %) are similar to those found in unprotected African infants of the same age living in other areas of Africa (Close, 1955: 10.7 %; Thompson, 1956: 16.7 %), and to the concentrations found in healthy European adults living in tropical Africa. (Edozien, 1957: 17.6 %; Busson *et al.*, 1953: 16.1 %). The precise significance of these findings remains to be assessed.

III. *Gamma-globulin levels at one and two years of age in malarious Gambian children and in children from the same environment protected from birth by continuous chemoprophylaxis (Slide II).*

The gamma-globulin values at one and two years of age in malarious and non-malarious children are shown in Table 2.

Table 2 — *Mean serum gamma-globulin values in protected and unprotected children aged 12 months and in the same children aged 24 months*

Subjects	Age 12 months		Age 24 months	
	No.	Gamma-globulin (%)	No.	Gamma-globulin (%)
Chloroquine Children	27	19.7 *	22	20.6 **
Pyrimethamine Children	32	18.8 *	23	20.9 **
Control Children	29	19.7 *	21	26.1 **

* Difference not significant.
** Difference significant.
Observed difference 3.75 standard error (chloroquine/control).
Observed difference 3.66 standard error (pyrimethamine/control).

COMMENT

It will be noted that at one year the gamma-globulin content of the serum of the malarious children does not differ significantly from that found in the protected children. At two years, however, the differences become significant.

IV. *Serum protein pattern at three, four, and five years in malarious Gambian children and in children from the same environment protected from birth by continuous chemoprophylaxis (Slide III).*

The mean serum protein values of malarious and non-malarious Gambian children for three successive years are shown in Table 3, together with their mean gamma-globulin levels. The results are compared with those of their respective parents and lactating women from the same area.

TABLE 3 — *Mean values of the different serum protein fractions (determined chemically), and of serum gamma-globulin (determined electrophoretically) in protected and unprotected Gambian Africans*

Description of group	Mean age in years	No. in group	Total protein (gm %)	Albumin (gm %)	Globulin (gm %)	Gamma-globulin (%)
Protected children	3	16	7.13	3.92	3.20	24.4
Unprotected children		13	7.59	3.83	3.76	32.2
Protected children	4	21	6.73	3.59	3.14	24.1
Unprotected children		13	6.87	3.21	3.66	28.1
Protected children	5	20	7.08	3.44	3.64	25.3
Unprotected children		10	7.38	3.59	3.79	31.4
Untreated parents of the protected children	—	20	7.00	3.00	4.00	33.9
Untreated parents of the unprotected children	—	20	7.04	3.10	3.94	32.6
Untreated lactating Gambian women	—	97	6.98	3.26	3.72	32.9

COMMENT

The mean serum gamma-globulin values are constant in the protected children. The striking result is the persistently higher gamma-globulin content of the serum of the malarious children. The gamma-globulin values in the unprotected children are significantly higher throughout the period of observation (observed difference 4.1 standard error at 3 years; 2.9 standard error at 4 years; 5.2 standard error at 5 years). It is interesting to note that the gamma-globulin level of the malarious children is similar to that of adults from the same area and to that found in the parents of both protected and unprotected groups.

V. *Gamma-globulin levels for two years of healthy lactating Gambian women protected from malaria (Slide IV).*

The gamma-globulin values of lactating Gambian women after one and two years of continuous malaria chemoprophylaxis are shown in Table 4. The results are compared with their own values before treat-

Table 4 — *Mean serum gamma-globulin values of lactating Gambian women before and at the 12th and 24th months of chemoprophylaxis contrasted with the mean values of untreated lactating women examined at the same times*

Subjects	No. in group	Gamma-globulin (%)	Standard deviation
Chloroquine mothers			
Before treatment	32	32.2 *	4.40
At the 12th month	28	29.0 *	3.67
At the 24th month	24	26.2 *	4.92
Pyrimethamine mothers			
Before treatment	33	33.8 **	4.95
At the 12th month	33	31.2 **	5.03
At the 24th month	30	28.2 **	4.40
Control mothers			
Initially	32	32.6	4.47
12 months later	30	31.2	5.19
24 months later	25	31.4	5.87

* Difference significant:
At 12 months: Observed difference 2.71 standard error.
At 24 months: Observed difference 4.69 standard error.
** Difference significant:
At 12 months: Observed difference 2.11 standard error.
At 24 months: Observed difference 4.67 standard error.

ment and those of a control group of lactating women from the same environment who were not given any antimalarial drugs.

COMMENT

It will be noted that after one year of treatment a significant drop in gamma-globulin concentration has occurred and that a further significant drop occurs on completion of the second year of chemoprophylaxis. It is interesting to observed that the gamma-globulin levels of the two groups before treatment were similar, and that in the control group of lactating women the gamma-globulin concentration has remained constant throughout the period of observation.

DISCUSSION

Evidence is slowly accumulating from various parts of Africa of the importance of malaria in the production of the raised gamma-globulin levels found in symptom-free Africans. Thus, Holmes *et al.* (1955) have suggested that in Uganda the degree of abnormality of the serum protein pattern corresponds more closely to the incidence of exposure to malaria infection than to the protein content of the diet. McGregor *et al.* (1956) in a controlled experiment, in which malaria infection was the only variable, demonstrated that three year old Gambian children possessed significantly higher mean gamma-globulin values than did a group of children from the same environment who had been protected from malaria from birth by continuous chemoprophylaxis. De Maeyer and Roels Broadhurst (1956) in the Belgian Congo found that children with a high parasite index (64 %) had higher gamma-globulin values than those with a low parasite index (4 %). The results of our investigations in the Gambia, which we have summarised (*loc. cit.*), leave us in no doubt as to the importance of malaria infection as a major aetiological factor in the production of the typical serum protein pattern found in symptom-free Africans. The significance of genetic and other environmental factors remains finally to be assessed (Slide V).

CONCLUSION

It is concluded that repeated malaria infection plays a major part in the development of high levels of serum gamma-globulin in young Gambian children and in the maintenance of these high levels throughout their adult lives. The possibility that this rise in gamma-globulin represents a specific immunological response should be borne in mind.

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O SISTEMA NEUROENDOCRÍNICO NO IMPALUDISMO

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O assunto do sistema neuroendocrínico no impaludismo oferece aspectos clínicos interessantes sob o ponto de vista do sector endocrínico, assim como do departamento vago-simpático.

Este problema tem merecido da escola médica brasileira estudos especiais demonstrando a participação do sistema neuro-endocrínico em muitos distúrbios observados na malária.

O impaludismo, outrora tão disseminado no Brasil, onde existiam alguns milhões de casos, está actualmente sobremodo reduzido, depois da benemérita campanha realizada pelo Prof. Mário Pinotti, hoje Ministro da Saúde, mediante, a princípio, o expurgo anofelino pela dedetização intradomiciliana, pondo em prática a opinião de Carlos Chagas (1905) da infestação malárica no domicílio e, ùltimamente, pelo sal cloroquinado, método original daquele sanatorista patrício. Graças a esta luta antimalárica, de que resultou a diminuição extraordinária de impaludados no Brasil, a verificação das perturbações neuroendocrínicas se tornaram mais escassas, mas o que se apurou até anos atrás patenteia, pelas apuradas observações então colhidas, quão comprometido se encontra este sistema nesta protozoose.

O sistema neuroendocrínico deve ser apreciado nas formas agudas e nas formas crónicas do impaludismo, pela variação que oferece a sua sintomatologia clínica.

Nas modalidades agudas da malária não as supra-renais que apresentam maiores distúrbios, caracterizados pela insuficiência glandular.

No Brasil, em Maio de 1914, o Prof. Clementino Fraga, da Baía, observou no seu serviço hospitalar um caso grave de impaludismo, que, vindo a falecer, o exame histopatológico, feito pelo Prof. Leôncio Pinto, revelou hipoepinofria, o qual descrevera alterações patológicas supra-renais provocadas pelo plasmódio.

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 217-231, 1959

Em seguida, foram observados mais quatro casos, que constam da tese de doutoramento do Dr. Armínio Fraga (1917), interno do Prof. Clementino Fraga, sobre «Insuficiência para-renal no impaludismo».

Este caso foi comunicado pelo Prof. Clementino Fraga, ainda em 1914, à American Society of Tropical Medicine, de Nova Iorque, por ocasião da sua décima quarta reunião anual.

Em Outubro de 1916, os médicos franceses do Oriente, Paisseau e Lemaine, publicaram no *Bol. et Memoires de la Soc. Med. de Paris* e depois na *Press Médicale* (Dezembro de 1916) importante trabalho relativo à insuficiência supra-renal na malária, confirmada pela necropse.

Em 1916 também o Prof. Miguel Couto, do Rio de Janeiro, fala em aula sobre a insuficiência supra-renal no impaludismo, a que chamou de síndroma de Fraga, e citando o trabalho de Barker (1895), sobre o assunto, o qual descreveu alterações patológicas das supra-renais pelo plasmódio do impaludismo.

Do interno do Prof. Couto saiu, em 1917, a tese de formatura do Dr. Joaquim Mota, sobre «Supra-renalite palustre», relatando cinco casos do serviço daquele professor e mais quatro estranhos.

Ainda no Brasil, além de outros, merecem ser lembrados os trabalhos de A. Mac-Dowell, Lobato Neto, Lopes Pontes, R. Faria de Andrade, Fernando São Paulo, Mário Furquim, Peregrino Júnior e Heraldo Maciel.

Antes, porém, destas publicações relativas ao papel das supra-renais no quadro clínico da malária, algo já se suspeitava da sua participação nos distúrbios desta protozoose.

Assim, os estudos de Sergent, sobre a hipoepinefria em dadas infecções; de Grall e Clarac (1910), que chegam a dizer que a astenia e a algidez de certas formas perniciosas do impaludismo aparecem e evoluem como na forma pura da insuficiência supra-renal e a que se junta, acrescentam eles, a hipotensão arterial; da mesma forma, Ascoli escreve «a baixa da pressão arterial, a pequenez do pulso, o vómito, a prostração, a astenia, o colapso, a pigmentação, os sintomas mais característicos da malária e os que a ela se seguem, representam quase tudo o quadro recentemente descrito, como da insuficiência supra-renal.

A insuficiência supra-renal do impaludismo se pode manifestar na sua forma pura, que é a síndroma de Sergent e Bernard, ou na modalidade clássica de Addison, em que se associa àquele síndroma a melanodermia.

Em suas linhas gerais, esta hipoepinefria se caracteriza pelo abafamento das bulhas cardíacas, hipotensão arterial, astenia neuromuscular, maior taquicardia na posição ortoestática (sinal de Fraga), distúrbios humorais e do metabolismo (principalmente natripenia, cloropenia e hipercaliemia), a que se pode juntar a melanodermia (de patogenia provàvelmente simpática).

Dos síndromas de hipoepinefria de origem palúdica tivemos ensejo de observar não poucos casos e deles vamos citar o primeiro por nós acompanhado, por ser bem frisante e seguido de necropse confirmativa: M. F. T., branco, 30 anos, entrou para o serviço clínico do Prof. Miguel Couto em 1910, com acessos febris intermitentes em dias alternados, revelando o exame de sangue a presença do plasmódio de Laveran, tipo terça benigna. O tratamento antipalúdico fez cessar a febre e desaparecer o hematozoário do sangue periférico. Queixava-se o paciente de grande astenia e a pele apresentava-se uniformemente bronzeada. A pressão arterial era de 78 m na máxima e 32 m na mínima. Ligeiro aumento epatolienal. A astenia acentuou-se cada vez mais, assim como a melanodermia, manifestando-se em placas nas mucosas labial e bucal. Seguiu-se extrema caquexia e, por fim, o desenlace fatal. O exame histopatológico das glândulas supra-renais revelou congestão pronunciada e hemorragia difusa em toda a camada cortical, com pequenos focos de hemorragia na zona fascicular desorientada e principalmente glomerular. Havia pigmento melânico disseminado por toda a glândula supra-renal. Este caso, que observámos em 1910, nós o olhámos, mas não percebemos a sua originalidade, a despeito de havermos escrito como diagnóstico impaludismo e hipoepinefria no livro de registo. Cedemos esta observação para figurar na tese de formatura (1917) do Dr. Joaquim Mota, o qual conseguiu publicar belas microfotografias coloridas muito elucidativas da etiopatogenia palustre.

Além destas síndromas clássicas e regulares das glândulas supra-renais, há ainda uma série de outras, chamadas anómalas, que se encontram também tendo como factor etiopatogénico o plasmódio de Laveran e das quais possuímos pessoalmente observações bem interessantes.

Em 1917, A. Mac-Dowell descreveu um quadro clínico na malária sobre as «Bradicardias hipotónicas e dos distúrbios supra-reno-simpáticos no impaludismo», isolando uma nova síndrama palúdica, caracterizada por hipotensão arterial, astenia neuromuscular e bradicardia, de que já falámos, e que denominámos «síndroma de Mac-Dowell», na qual existe hipoepinefria, associada à baixa do *tonus* do simpático e prevalência acentuada da tenacidade vagal, pela acção da toxina malárica, de que resulta o *pulsus tardus* de 60 e até mesmo 42 batimentos por minuto. J. Mota observou vários casos pessoais, assim como nós mesmo.

O que diferencia esta síndroma de Mac-Dowell das clássicas de hipoepinefria, onde se nota a taquicardia, é a bradicardia bem pronunciada e que a individualiza.

No meio das formas perniciosas da malária há um grupo em que a participação das glândulas supra-renais é observada, de parceria com o sistema neurovegetativo; assim as modalidades:

1) *Álgida,* na qual se notam distúrbios gastrintestinais profundos, algidez geral, prostração e grande hipotensão, colapso periférico, tendência à síncope, por vezes fatal.

2) *Diaforética,* quase sempre acompanhada de algidez, abundante sudorese, na qual os nervos secretores cutâneos entram em cena.

3) *Assistólica,* em que predominam os sintomas dependentes da insuficiência cardiovascular, para cuja patogenia contribui a camada medular, pela carência de adrenalina, nela formada.

4) *Gastrintestinal,* cujo quadro clínico se manifesta por vómitos por vezes incoercíveis, distúrbios intestinais coleriformes e desenteriformes, com grande desidratação. Peregrino Júnior cita uma grave epidemia de malária, coleriforme em zonas epidémicas de Santarém (Pará), de alto índice letal, para o qual contribuiu o estado carencial da população atacada.

5) *Pseudo-abdominal,* pseudoperitonite e pseudo-apendicite, nas quais se torna necessário um pronto diagnóstico palúdico, para que não se chegue ao acto operatório de urgência. No nosso serviço da Clínica de Doenças Tropicais e Infecciosas possuímos um característico caso destes, acompanhado pelo assistente Dr. Genard Nóbrega, que a respeito publicou um interessante trabalho. Eis o resumo da observação: Olinda B. de S., brasileira, professora, parda, casada, de 36 anos, vinda de zona palustre, doente, entrou na enfermaria com fortes dores abdominais, mais na fossa ilíaca direita, com vómitos. Temperatura elevada, taquicardia, calafrios, cefaleia, ventre contraído e doloroso. Tudo, pois, falava a favor de peritonite e do acto cirúrgico, mas a procedência da

doente levou ao exame de sangue, que revelou grande número de formas jovens e adultas do *Plasmodium falciparum,* confirmando-se assim a suspeita do nosso assistente. Instalada a medicação antimalárica, a paciente começou a melhorar e ao cabo de sete dias o quadro abdominal desapareceu e finalmente a doente teve alta, curada de seu impaludismo, sem fazer nenhuma operação.

Sobre esta forma palúdica pseudo-abdominal existe o trabalho de Bressot e de outros autores. Com relação à sua patogenia, parece residir na hipoepinefria, acompanhada de sérios distúrbios neurovegetativos abdominais, sendo estes apontados por Castellani.

Outra forma clínica da hipoepinefria que se pode notar no curso da malária aguda é a *encefalopática,* estudada por Leignel Lavastine, a qual se caracteriza por astenia psíquica, abulia, dismnésia, estado melancólico, estado confusidinal, depressivo, apático, etc., em que predomina o acometimento da camada cervical das supra-renais. O Dr. Luís de Melo Mota observou um nítido caso desta modalidade e de origem malariana.

Há ainda a modalidade apoplectiforme, estudada por Arnand e outros autores, devida a hemorragia fulminante das supra-renais, mais frequente em crianças e nas doenças por bactérias, tal como a síndroma de Waterhouse-Friederinschen na meningite cerebrospinhal, mas que já foi também observada no impaludismo pernicioso, tal como conseguiu Pende e foi verificado por Brunelesch, em necropses de formas fulminantes de malária.

Joaquim Mota cita Kelsch, que escreveu uma caquexia primitiva hidrémica, que mais tarde Grall chamou de forma febril da caquexia primitiva, com anemia grave, acessos febris, sem albumina. Sabatier fala de grande astenia de tais doentes. Paisseau e Lemaire observaram numerosos destes casos, demonstrando o papel das supra-renais na sua patogenia, ainda que não exclusivo, e denominaram tal síndroma de caquexia aguda do impaludismo primário. Ao cabo de seis a oito semanas estabelece-se a caquexia, que surge ràpidamente e com o êxito letal, e a necropse revela, pelo exame anatomopatológico, alterações em várias vísceras, principalmente a medula óssea e as supra-renais.

Além destas síndromas agudas supra-renais consignadas no impaludismo, são também observadas as chamadas formas frustas, oligossintomáticas, esboçadas de hipoepinefria, a que Sergent denominou de debilidade supra-renal, nas quais surgem sinais ou sintomas apagados, escassos ou mesmo isolados, tal como estudaram Annes Dias e Peregrino Júnior, no Brasil.

Na fase tardia ou crónica do impaludismo, ou em pleno estado de caquexia palúdica, as supra-renais compartilham também na síndroma que então se manifesta, sob o quadro clínico da velhice precoce ou prematura, a progeria de Gilford, ou tão-sòmente numa forma menos pronunciada da gerodermia de Apert. Esta síndroma manifesta-se, na criança, pela hipo ou atricose, pele de velho, astenia, tristeza, hipoplasia gonadal, etc., tendo como selo da malária, além dos antecedentes febris palúdicos, a clássica esplenomegalia fibrosa, acompanhada de anemia hipocrómica.

Não raro, após os acessos febris de impaludismo desaparecidos e os doentes clìnicamente curados da plasmodiose, permanece neles um estado de astenia, que se prolonga sobremodo, demorando em estado de miopragia ou, melhor, de hiponefria frusta e latente, a que Galeno de Carvalho denomina, em adequada expressão, de preguiça parapalúdica, tal como se observa entre os sertanejos do interior do Brasil.

Se passarmos a apreciar as demais glândulas endocrínicas, veremos que a sintomatologia clínica delas depende, mais se manifestando na cromicidade da malária que na sua fase aguda.

Com relação à tireóide, D'Arnand, Gerken e Hume descreveram casos em que verificaram fenómenos de hiperfunção desta glândula, no impaludismo agudo. Julgamos, porém, que este hipertireoidismo notado tem como factor patogénico uma predisposição individual latente, que se desencadeia em síndroma basedowiana sobre a influência da actuação da toxina palúdica.

Mais frequente, porém, é o hipotireoidismo, como temos observado no impaludismo crónico e na caquexia malariana, onde a baixa da função desta glândula é patente, salientando-se o aspecto mixadematoso e a diminuição do metabolismo basal, além de outros sinais.

No que concerne às paratireóides, ainda se não tem apurado bem o seu comportamento no impaludismo. Assim, Hebert e Block observaram, num caso de malária, a tetânia, denunciando a insuficiência destas glândulas. Parece, todavia, ser mais frequente a hipertireoidia, em vista da hipercalcemia que se verifica mais vezes na malária, como encontrou Heraldo Maciel, de que resulta a descalcificação observada nos impaludados.

As gónadas pagam o seu tributo, igualmente ao impaludismo, mas quase tão-sòmente quando crónico.

Quando a malária se cronifica na criança masculina antes do seu período de puberdade, os testículos mostram-se pouco desenvolvidos, a bolsa escrotal retraída, certa microgenitossomia, ausência ou diminuição grande da pilosidade puberal, a voz e a mentalidade permanecem infantis.

Se a criança é do sexo feminino, quando chega a época da puberdade, as regras tardam, podendo haver dismenorreia ou mesmo anemorreia, os seios mostram-se pouco desenvolvidos, permanecendo o infantilismo.

Se a cronicidade palúdica sobrevém já na pessoa adulta, pode sobrevir deficiência gonadal, tendo como consequência um estado de infantilismo regressivo, em ambos os sexos.

A glândula hipofisária ainda não foi estudada no impaludismo. Apenas um dado infantilismo consignado, por vezes, na juventude, em presença de malária crónica, faz lembrar o de origem hipofisária, pela magreza e alongamento dos braços e das pernas, pela permanência das cartilagens epifisárias, do hipogenitalismo. Clark e Temlissen, citados por Mark Boyd, encontraram, em necropses, a presença de parasitas do impaludismo no interior de capilares da hipófise, em casos malignos.

Síndromas pluriglandulares podem ser observados na fase crónica e na caquexia palúdica, podendo mesmo dizer-se que, ao lado da esplenomegalia e da anemia grave, o quadro clínico do factor poliendocrínico constitui principalmente estas síndromas.

Temos tido ensejo de verificar tais síndromas multiglandulares na malária não tratada ou mal tratada, nas quais a patogenia reside na insuficiência tereóide, gonadal, supra-renal e provàvelmente da hipófise.

Mais vezes, tais síndromas se evidenciam pelo infantilismo pré-puberal ou mesmo serôdio, e nelas se manifestam sinais e sintomas, mais ou menos acentuados, decorrentes da interferência patogénica das diversas glândulas endocrínicas. C. Correia da Costa escreveu a sua tese de formatura sobre o «Infantilismo entre nós» (no Brasil), na qual estuda o assunto, com observações próprias, nas quais a malária se apresenta como etiologia.

De Blum descreveu numerosos casos em que logrou encontrar o plasmódio de Laveran no sangue.

Foley e Parrot, na Argélia, assim como Montel e Dang Van Cuong, citam as suas observações de síndromas pluriglandulares palustres.

Chimissé consignou casos de infantilismo na mulher, com puberdade surgida tardiamente aos vinte anos, assim como órgãos genitais infantis, hipomastia e psiquismo atrasado.

ANATOMIA PATOLÓGICA E PATOGENIA

O estudo apurado das necropses realizadas em casos de impaludismo com manifestações clínicas endocrínicas vem confirmar, pelas lesões glandulares verificadas, a sua patogenia.

Assim, no nosso primeiro caso de hipoepinefria, a necropse revelou, conforme já o descrevemos anteriormente, congestão pronunciada e hemorragia difusa em toda a camada cortical, com pequenos focos hemorrágicos na zona fascicular, que se mostrava desorientada, e principalmente na glomenular. Havia pigmento melânico disseminado por toda a glândula supra-renal.

Na observação primeira do Prof. Clementino Fraga, o laudo da necropse feita pelo Prof. Leôncio Pinto declara haver desaparecimento dos espongiócitos da zona glomenular e parte da fascicular, congestão da camada cortical, com grande quantidade de pigmento. A camada medular mostrava-se ligeiramente congesta.

Num dos casos de Joaquim Mota havia congestão e pequenas hemorragias nas camadas cortical e medular, diminuição do tecido cromafino, grande foco hemorrágico no limite das duas camadas, desorientação da fascicular, pigmento melânico em grande quantidade espalhado por toda a glândula.

Armínio Fraga descreve, num dos seus casos, o seguinte: congestão e ligeiras hemorragias. Células endoteliais dos capilares contendo pigmento melânico. Aspecto espongiocitário na zona reticulada, na qual algumas células continham pigmento melânico e ocráceo.

Clark e Tombisson, citados por Mark Boyd, encontraram em necropses parasitas de Laveran nas glândulas tireóide, paratireóide, hipófise e supra-renais no interior dos capilares em casos malignos de impaludismo, mas sem fenómeno de fagocitose local.

Brunelesch verificou, na terça benigna, formação de histrócitos fagocitários nas células endoteliais dos sinusóides da hipófise, mas pouco pronunciados.

Nas supra-renais encontrou algumas manifestações nítidas ao exame microscópico. Nas formas agudas fulminantes havia baixa da substância lipóide da camada cortical. Em outros casos pouco marcada congestão dos capilares por hematias parasitadas. Pigmento melânico fagocitado foi encontrado nos grandes macrófagos entre os capilares e no estroma glandular.

Paisseau e Lemaire encontraram em todos os seus casos de hipoepinefria palúdica manifestações de supra-renalite aguda degenerativa ou hemorragias.

Com relação à patogenia destas síndromas endocrínicas de origem palúdica tem sido verificado que não só o hematozoário da terça benigna (*Plasmodium vivax*), como também, e principalmente, o da maligna (*Plasmodium* precoce ou *falciparum*) podem ser a causa das lesões glandulares observadas.

Neste acometimento endocrínico, no que se refere às supra-renais, tem sido consignada a presença de plasmódios e de melanina no interior dos capilares, constituindo embolias parasitárias e pigmentárias; estados congestivos, pequenos focos hemorrágicos e, com menos frequência, foco maior de hemorragia com destruição do parênquima gladular. Degeneração celular e, por vezes, com presença de pigmento ocre, a hemossiderina.

Nas demais glândulas endocrínicas têm sido verificadas, de preferência, embolias parasitárias e pigmentárias, assim como congestão e pequenas hemorragias. O granuloma de Dürck, que se encontra nas formas perniciosas nervosas, principalmente comalosa, não foi assinalado nas glândulas endocrínicas na malária.

DISTÚRBIOS HUMORAIS E METABOLISMO

Esses assuntos merecem ser apreciados na insuficiência supra-renal no impaludismo, pela importância que adquirem nesta síndroma endocrínica.

Do estudo realizado a respeito no estrangeiro, assim como no Brasil, principalmente pelos professores Annes Dias, Peregrino Júnior e outros pesquisadores, podemos apresentar os seguintes dados sobre os distúrbios humorais e o metabolismo nas endocrinopatias palúdicas:

Cloropenia
Natropenia
Hipercaliemia

Ascorbiopemia
Hipoglicemia
Hipersensibilidade à insulina
Hiperazotemia não proteica
Hipersulfuremia
Alta do ácido lático sanguíneo
Alta de magnésio plasmático
Hipoadrenalinemia
Hipocorticosteronemia
Baixa da reserva alcalina (acidose)

Da hipotireoidia resulta a baixa do metabolismo basal e da hiperparatireoidia a hipercalcemia e a alta das fosfatoses.

SISTEMA NEUROVEGETATIVO NO IMPALUDISMO

Se muitas são as manifestações endocrínicas na malária, não menos numerosos são os distúrbios vago-simpáticos verificados nesta protozoose.

Estes estudos têm merecido a atenção da escola médica brasileira, que a respeito chegou a interessantes conclusões.

O comportamento do complexo vago-simpático no impaludismo pode ser feito mediante provas experimentais, assim pelo apuro da sindromatologia clínica, apreciando-se os distúrbios observados na malária, oriundos do sistema neurovegetativo.

Henrique Duque, J. G. Sousa Sobrinho, A. Mac-Dowell, mediante a pesquisa pelas injecções de adrenalina, atropina e pilocarpina, segundo o método de Eppinger e Falta, para se avaliar o tonismo neurovegetativo, e após reiteradas investigações, chegaram a conclusões sobremaneira interessantes, apurando que no impaludismo pode existir um estado de anfotropismo vago-simpático; sendo, porém, mais vezes observada a vagotonia, tal como se verifica sob o ponto de vista clínico, onde o reflexo oculocardíaco de Achner é positivo em 50 % nos impaludados.

Estas investigações experimentais foram ulteriormente repetidas por M. Paula Fonseca, que as confirmou, e de grande valor foram as deduções a que conseguiu chegar, sob apurado determinismo, as quais podem ser resumidas nos seguintes itens: 1) vagotonia crescente até o auge do paroxismo febril; 2) a simpaticotomia faz demorar o período de incubações, retardando os acessos febris primários; 3) a vagotonia favorece serem os acessos febris regularmente intermitentes; 4) a simpaticotonia dificulta a intermitência regular dos acessos febris; 5) as perturbações gástricas (náuseas, vómitos, etc.) resultam mais de hipervagotonia que da quinina pela via bucal; 6) a simpaticotonia nos impaludados, havidos clìnicamente como curados, parece ser índice seguro de cura radical, não mais surgindo geralmente a recaída; 7) a anfotonia vago-simpática, e principalmente a vagotonia, em doentes clìnicamente havidos como curados da malária, parece indicar não ser real a cura, estando sujeitos à recaída.

Não precisamos encarecer e realçar o valor destas conclusões no estudo e na clínica do impaludismo.

No curso do acesso regular de malária há uma série de sinais e sintomas que, devidamente apreciados, se explicam como manifestações de patogenia neurovegetativa.

Assim, os calafrios iniciais, de origem vasomotora, por vasoconstrição periférica e vasodilatação interior ou visceral, as quais, geralmente, se traduzem nas crianças por ataques convulsiformes.

A secura da pele no início do acesso febril e a sudorese no declínio, como demonstrações patentes secretonas, dependentes do complexo vago-simpático.

Na análise de casos de impaludismo, quer provocados pelos plasmódios das formas benignas, quer pela maligna, não raramente se observam manifestações mórbidas que se enquadram como sendo havidas de perturbações funcionais e mesmo devidas a comprometimento somático do sistema neurovegetativo.

Em centenas de impaludados que tratámos ou examinámos, tivemos ensejo de encontrar distúrbios interessantes de patogenia do sistema vago-simpático e que bem demonstram a sua participação no quadro clínico desta multiforme protozoose. Nesta observação pessoal tivemos a confirmação do que já havia sido consignado por malariologistas estrangeiros e nacionais, assim como nos foi dado acrescentar algo de novo a respeito do assunto.

Começando pelas discromias cutâneas, surge desde logo a melanodermia da síndroma de Addison palustre, verificada por inúmeros autores e por nós mesmo. A sua origem simpática, a despeito da sua distribuição não ser simétrica, e sim disseminada sem orientação ou generalizada, é, geralmente, admitida, ainda que com a concomitância de outros factores patogénicos.

Cyanodermia simétrica, de origem palúdica, constitui caso singular, que observámos em 1925 na 7.ª enfermaria, do Prof. Miguel Couto, na Santa Casa da Misericórdia (Rio de Janeiro). Observação pela primeira vez descrita, e que denominámos *Cyanodermia simétrica palúdica*, a que atribuímos a uma patogenia neurovegetativa.

Eis o resumo da observação: A. G. S., brasileiro, pardo, 14 anos, com impaludismo apanhado em Merity (zona malariana), diagnóstico confirmado pelo exame hematológico, que verificou a presença do *Plasmodium vivax*. No início a febre era diminuta, chegando depois a 41°. Ao entrar para o serviço clínico, o doente já apresentava numerosas manchas espalhadas simètricamente pelo corpo, de coloração acentuadamente azul, não se modificando pela pressão, isto é, não se descorando ou mudando de cor pela compressão nem tão-pouco sofrendo alteração pelo esforço ou cansaço físico. Sobre tais manchas azuis não havia secreção nem distúrbios tróficos, nem perturbações da sensibilidade ou da temperatura. Achavam-se distribuídas pela face, onde eram mais intensas na sua cor azul, nas regiões genianas, no queixo, nas orelhas, no tronco, no peito, nos braços e nas pernas, sempre simètricamente, sendo que até nas palmas das mãos e nas plantas dos pés eram encontradas. Ao cabo de algum tempo passavam tais manchas ao roxo-amarelado, o que começava pelo centro. Eram arredondadas, elípticas ou em anel. Essa cianodermia era adquirida e sem caracteres hereditários ou familiares.

O doente teve alta curado do seu impaludismo após três semanas de tratamento e algo melhorado da cianodermia, que desapareceu com a medicação da adrenalina.

Cumpre-nos declarar que, após um ano que acompanhámos o doente, tivemos a tristeza de vê-lo vítima do mal de Hansen, em sua forma nervosa.

A patogenia simpática parece-nos acertada pela simetria e metameria da cianodermia observada, a qual melhorou e desapareceu com o emprego da adrenalina, como dissemos há pouco, assim como sabemos que o simpático tem grande influência sobre certas células da pele, chamadas cromatóforas e melanoblastos, que têm papel importante na coloração cutânea.

Não eram as manchas provenientes de distúrbios vasomotores, e sim da pigmentação da pele; nem tão-pouco eram isoladas ou espassadas, sem orientação, como acontece quando congénitas, de que possuímos dois casos, e nada tinham com a mancha azul-mongólica dos nossos ameríndios e menos ainda com certas tatuagens artificiais.

Quanto à etiologia dessa cianodermia simétrica adquirida, julgamos residir no impaludismo, pois só apareceu em seguida ao paciente apanhar a malária, como também as manchas azuis se exacerbaram com os acessos febris intermitentes, para finalmente desaparecerem com o tratamento antipalúdico, coadjuvados pela adrenalina.

A hipótese de uma etiologia, que poderia estar em causa, pelo facto de ulteriormente, posto que tardiamente, se manifestou o mal de Hansen, não nos parece tão plausível, pois esta doença só se apresentou um ano depois e mais quando o paciente possuía a sua cianodermia simétrica não tinha manifestação alguma que fizesse suspeitar morfea; e, mais, nas manchas ou fora delas não foi percebido, ao exame cuidadosamente feito, nenhum distúrbio ou dissociação da sensibilidade, o que, geralmente, é precoce em tais casos de lepra. Procurámos algo a respeito na bibliografia sobre malária e encontrámos, apenas em Ascoli, a citação da revista médica *Lo Spallanzani*, de 1899, o que ele chamou de «mancha azul de Longo», mas não apresentou a sua descrição.

Como manifestação de demografismo há a linha branca de Sergent, encontradiça nas formas supra-renais da malária, como os autores têm consignado e nós também verificámos.

Os distúrbios vasomotores no curso do impaludismo são múltiplos e notam-se amiúde, como a microsfigemia, o angiospasmo, a palidez e o resfriamento das extremidades, a acrocianose, a instabilidade do pulso, etc.

O Prof. Abreu Fialho verificou isquemia e hiperenia retiniana palúdicas e também amaurose transitória, de 1 a 2 horas, durante o acesso febril e a enxaqueca oftálmica.

Bassères cita um caso pessoal de acrocianose intermitente de origem palustre, localizada mais nas mãos que nos pés, com sensação de frio, formicamento, dormência e mesmo dor, nas extremidades. Estas manifestações acompanhavam os acessos febris.

No impaludismo notam-se, como nós mesmo temos encontrado, manifestações de parestesias, associadas ou não a fenómenos dolorosos, de carácter paroxísmico, de disposição simétrica e localizados, de preferência, nas extremidades. Assim, sensações de formicamento, de dormência, de urência, de frio, principalmente nas pernas e pés, assim como nos braços, constituindo as chamadas acroparestesias.

A causalgia, qual dor que queima ao mesmo tempo, foi assinalada por Grall e por Le Dantec.

A acromelalgia, que, sendo acompanhada de hiperemia, constitui a eritromelalgia de Weil-Mitchell, de que falam Joyeuse e Sicé em impaludados observados por médicos franceses na Macedónia e no Oriente (1916-1918).

Como distúrbios tróficos, além da pele de galinha ou anserina, têm sido verificadas na malária lesões profundas de mal perfurante, de gangrena das extremidades ou síndroma de Raynaud.

Tais síndromas neurovasculares palúdicas foram discutidas pelos próprios Raynaud, Marchand, Lunsbry, Rei, Manoni, Charpenter, Falguier, Béhier, Fischer, Kimelewky, Hare, Calmette, Mourson, Petit, Vernnil, Mouro, Boinet, Cassirer, Thayer, Leger, Pozzilli e Parsseau e Lemaire. Mouro, em seus 180 casos de síndroma de Raynaud, 15, ou 8,3 %, apresentaram antecedentes seguros de impaludismo, ao passo que tão-sòmente 28, ou 15,6 %, estavam completamente isentos de qualquer suspeita palustre anterior.

Segundo Laveran, ora a asfixia local se mostra intermitente, aparecendo tão-sòmente no acesso febril palúdico, ora persistente ao paroxismo febril e toma, então, carácter grave, podendo chegar à gangrena simétrica.

Hamanond, em 1912, descreveu dois casos pessoais interessantes, de síndromas de Raynaud, sendo o primeiro em hindu, de 19 anos, com malária aguda maligna, de marcha rápida e ascendente nos membros inferiores, sendo a perna direita amputada no joelho e também o pé esquerdo, conseguindo assim escapar.

O outro caso era de maometano, de 25 anos, com acessos febris típicos de malária, microsfigmia manifestando o quadro clínico de febre perniciosa álgida. Seguiu-se célere gangrena das extremidades, a qual se tornou séptica, vindo o doente a falecer. Gungomarah, Fullex e Allani (1932), citados por Joyeuse e Sicé, falam em asfixia súbita dos artelhos num caso de malária maligna, que impôs a amputação dos pedartículos.

Estes fenómenos de asfixia local, quando ligeiros, podem ser intermitentes, acompanhando o acesso febril.

Em 1920, Brossier, prosseguindo os estudos de seu mestre Monier--Vinard, descreveu uma síndroma funcional de origem palúdica, com 64 observações, que se caracterizavam por astenia, mais ou menos profunda, fadiga rápida, cãibras, mioclonias, ora com reacção masténica, ora miotónica, exagero, e mesmo trepidação, dos reflexos tendinosos, sensação de criestesia, hipostesia, até mesmo anestesia, de disposição radicular, distúrbios vasomotores (acrocianose, dermografismo, linha branca, hipotensão arterial, etc.), anemia, esplenomegalia.

Acredita Bossier que a patogenia de tal síndroma palustre seja nos nervos motores dos cornos anteriores da medula. Julgamos nós que esta síndroma de Brossier é mais fruto de epimefria, com participação neuro-vegetativa, que pròpriamente medular, sendo só a favor desta o *clonus* dos reflexos.

Ainda há no impaludismo um sinal de origem neurovegetativa, qual seja o reflexo pilomotor de André Tomás, que consiste no eriçamento dos pêlos no momento do paroxismo febril.

O Prof. Miguel Couto e o Dr. Francisco Tajardo (1899) observaram interessante caso de impaludismo, com acessos febris diários, durante meses, com polinevrite, apresentando mialgias espontâneas, reflexos tendinosos abolidos, amnésia, taquicardia acentuada.

Vindo a falecer, feita a necropse, o exame histopatológico dos nervos revelou a degeneração dos nervos ciático, papliténs internos e externos, tibial anterior, safeno externo, mediano cubital e pneumogástrico.

Tal caso constitui uma interessante observação de malária prolongada com vagoplegia, de que resultou a predominância da taquicardia, que vem, mais uma vez, demonstrar a acção fenadora vagal sobre os batimentos do coração.

THE TEACHING OF MALARIA DIAGNOSIS

A. J. Walker

In 1948 I wrote a paper entitled «The Teaching of Malaria Diagnosis» [1] in which the principles contemplated in this present paper were first described. At that time I had a considerable number of paretics under daily supervision. It was easy to prepare slides, each containing five thick blood filmes taken at 12-hour intervals. At the same time miniature thin blood smears were placed transversally on a single slide for the first 4 specimens. These thin preparations were extremely difficult and tedious to make; in order to have them uniform many were wiped off and replaced several times. They were used with two successive classes and then discarded. The medical students simply refused to spend their time searching these thin smears merely to see parasites in red blood cells, when it was so easy to inspect the parasites so readily found in the thick blood films.

Visits to different countries of Latin America revealed that, although some thick films were used, species diagnosis was not attempted, except with a thin blood smear, and most workers in malarious areas had their own concept of species significant forms derived from thin blood smear appearances. Their examination of a blood specimen consisted of searching until two or three of these so-called typical forms were encountered. No further examination was carried out to confirm this sketchy diagnosis nor to verify the non existence of another species such as the presence of falciparum gametocytes. To avoid the loss of time required for making and examining a thin blood smear in addition to the thick film, it was decided to eliminate the former and base diagnosis on the thick blood film alone. This step involved complete abandonment of all reference

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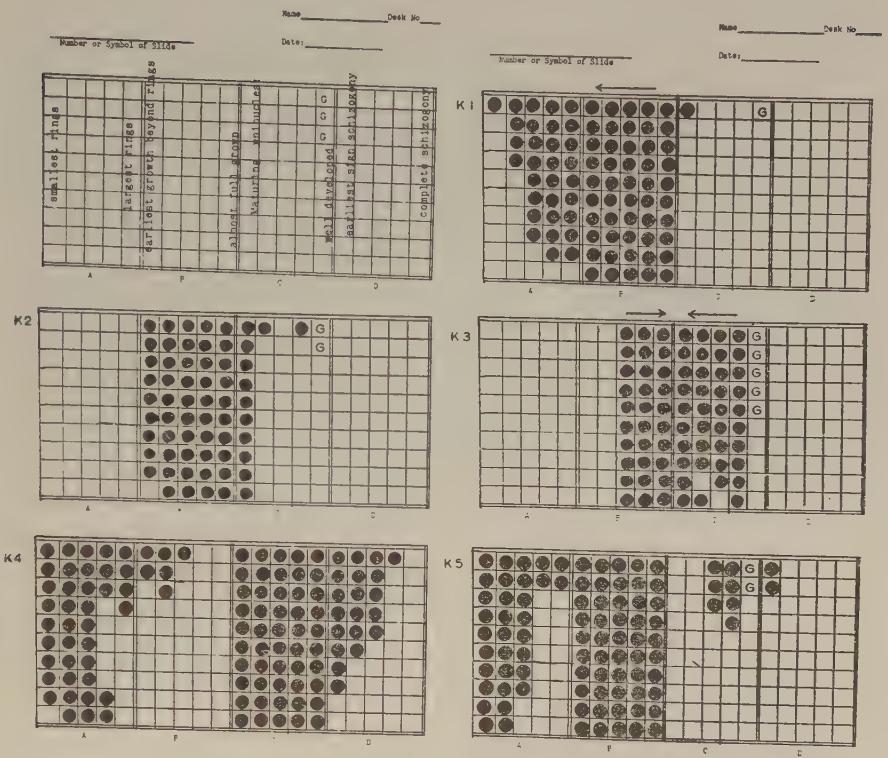
[1] Reprint from *The American Journal of Tropical Medicine*, vol. 28, n.º 6, Nov. 1948.



to the containing cell and other features of the thin smear which had been used for many years, and to replace these with an entirely new philosophy of species diagnosis based only on the thick blood film.

An attempt was then made by means of daily or twice daily thick blood films, of an active infection to show that each species in its development gave a true and constant picture. *Falciparum,* for example, always appeared in the form of small, medium or large rings, the numbers of which could vary enormously within hours. Gametocytes seldom appeared before 8 to 12 days had elapsed and they could persist for many days after the last asexual forms had disappeared.

In different specimens the *vivax* infection could show at one time a relatively large proportion of the developmental cycle. The variations of the growing mid-cycle forms were fantastic, but at no time were rings alone encountered. In bloods in which rings appeared very numerous, careful examination showed that very many of these small forms were already demonstrating early pseudopod-like processes and were accompanied by scanty numbers of late stages of the cycle.

P. malariæ was so slow in its growth that 24-hour intervals between specimens were sufficient to show that growth and development went steadily on, that pigment was acquired shortly after the ring stage and became increasingly prominent. The mid-cycle forms were never irregular or distorted although the late stages were frequently influenced by abnormalities of the containing red blood cell.

P. ovale appears to be like *P, malariæ* surrounded by the pink schuffner staining in well stained preparations.

By this approach it has been possible to eliminate any detailed study of thin blood smears. These are reserved for instructional use only. Students without previous microscopic experience have diagnosed correctly the three species, as well as uninfected bloods, at the end of a concentrated course lasting two the three weeks. Their training is based on abundant well-stained material, which can only be obtained from cases of induced malaria. There exists one considerable disadvantage, it is hard to preserve thick blood films under coverslips for longer than 18 to 24 months. The teaching material, therefore, requires constant renewal. With the new mountingmedia it is hoped that slides may be conserved for a much longer period.

A rather simple teaching maneuver has been developed as a study procedure and not a part of the diagnostic examination. Where time permits it, the student is provided with a rectangle drawn on paper and divided into 200 small squares, 10 by 20. Each section of 50 squares is marked: A, B, C, D, from left to right. Instead of making detailed drawings of individual parasites, the student is invited to review a section of the thick blood film and place a check mark in the appropriate square, *as each parasite is encountered.*

Section A is to contain only ring forms, the youngest being placed in the left-hand column, the oldest in the right-hand column and intermedia forms in between. If one perpendicular line of 10 becomes filled with its type form the next adjacent square is used. If these are numerous, an arrow is placed below that portion of the diagram pointing to the squares these check marks would otherwise have occupied.

Unless it is desirous to record the proportion of gametocytes to rings, such a diagram is useless with falciparum and serves no useful purpose, except when sections A, B, A are used to record small, medium and large rings and to show the proportion of each.

Section D is for all forms of schizogony. The left-hand row to include the earliest traces of division of the nucleus of well grown parasites and the right-hand row complete division.

Section C is for the fully grown parasites. The gametocyte may be noted by the letter G in the right-hand column, instead of a check mark. The left-hand column can include somewhat irregular forms of *vivax* which will soon round up.

Section B includes all the growing forms; those most resembling rings in the left-hand column, those nearest to maturity in the right-hand column. The degrees between these are noted in the remaining three rows. The student places a mark in the square which most closely indicates the stage of the parasite observed, and continues to do so with each successive parasite encountered in the thick blood film in its appropriate position on the diagram until 5 adjacent perpendicular columns are filled.

These five columns represent the developmental stage of the majority of the parasites in that particular drop of blood and show when the next schizogony is likely to occur. The numbers of squares checked in the other three sections show if more than one brood is present. If there is a single brood, one section is usually completely vacant. Obviously this diagram is of no use with falciparum, where only section A would be operated. It is repeated for emphasis that this is not a method of diagnostic examination, but merely a study procedure.

The pattern resulting from the above study clearly shown the smallest and largest developmental forms present and the stage of the majority. The student, therefore, rapidly acquires an awareness of the number of ring forms which may be expected when the majority are almost fully grown, and *vice-versa,* how many advanced forms can be expected when the majority have only recently left the ring stage.

In other words, the thick film diagnosis consists of a review of a sufficient number of parasites which will enable the observer to note the smallest and largest parasites present, as well as the size of the most numerous. This has been termed by some, «The Panoramic Method of Diagnosis».

Since gametocytes appear promptly in *vivax* infections, and disappear simultaneously with the asexual forms, whether spontaneously or with drugs (this holds for *P. malariæ* as well, even though gametocytes are very infrequent) there is little point in stating the presence of trophozoites, gametocytes, schizonts, etc.

The initials V & M imply that a wide variety of stages may be seen at all times. With falciparum the situation is entirely different, three separate stages of the infection may be seen in an individual blood. Rings only, rings and gametocytes together, and gametocytes alone, which can be diagnosed as follows: F, F+g, and Fg.

SPECIES DIAGNOSIS OF MALARIA WITH THE THICK BLOOD FILM ALONE

Thin blood smears are no longer necessary for the species diagnosis of malaria. The combined thick film — thin smear originated at a time when thick blood films were much inferior to those of today. The use of thick — thin preparations implies that the thin smear is still essential. Thus the thick film becomes scondary and is neglected. As more skill is required to make a good thin smear the student gives all his attention to it, with the following findings of one eradication program.

100 slides	16	no thick film
	22	useless for different reasons
	29	poor, required prolonged examination
	35	satisfactory.

Before 1940 considerable practice was needed to correctly diagnose species by thick film. Field's stain did much to increase the appreciation of thick films. Variations and adaptations of the principle of the method gives such clean appearance to the preparations that tiny, irregular or large dense parasites are clearly visualized in the comparatively clean background.

The daily study of thick blood films of untreated infections in paretics permits the observation of the changing aspects of the infections. For teaching purposes, five thick blood films, taken at 12-hour intervals were placed on the same slide and examined in order. The proportion of the different developmental stages varied constantly in *vivax* and *malariae*, while in *falciparum* only a great variation in total numbers occurred.

Species diagnosis depends on an adequate knowledge of the behaviour of the infection in the peripheral blood rather than the recognition of a number of so-called type forms. The teaching endeavours to emphasize that the variation of constantly growing parasites is virtually limitless.

THE EFFECT OF A DIET DEFICIENT IN FACTOR 3, VITAMIN E AND CYSTINE ON THE COURSE OF *PLASMODIUM BERGHEI* INFECTIONS IN MICE

G. R. Coatney and J. Greenberg (U. S. A.)

These experiments were done to determine the effect of a diet deficient in factor 3 on the course of *Plasmodium berghei* infections in mice. Weanling BALB/cAnN × DBA/2JN F_1, males and females, born of mothers fed a ration deficient in tocopherol, were fed a ration deficient in vitamin E and containing large amounts of Torula yeast. This diet produces marked necrotic changes in the liver and muscles of the mice. Half the mice were on the diet 30 days and half for 40 days before inoculation with *P. berghei*. Approximately the same numbers of the same hybrid mice were fed an adequate synthetic ration and served as controls.

The deficient diet produced two significant differences in the course of the infection as compared with adequate rations: 1) the mice on the experimental died in about 15 days; those on adequate rations died in about 21 days; 2) the mice on the experimental diet had maximum infections of mature erythrocytes at the end of the first week which did not exceed 5 %; those on adequate rations had infections of mature erythrocytes 2 to 3 times as high.

The course of the infections in immature erythrocytes was similar in the two groups of mice. The results with mice on the deficient diet for 30 days were approximately the same as those with mice on the same diet for 40 days. There appeared to be no significant difference in the responses of the sexes.

Note — Full paper published in the *Journal of Parasitology*, **47**: 601-604, 1961.

GENERAL DISCUSSION

Dr. SCHNEIDER (France) — Je peux répondre en partie à la question concernant l'emploi de la primaquine sur le rythme hebdomadaire dans le traitement du paludisme à *P. vivax*. Depuis 20 ans, à la suite des travaux de Ph. Decourt, les malariologues français sont familiarisés avec l'emploi d'une association d'un schizonticide (mepacrine puis chloroquine) et d'une amino-8-quinoleine (pamaquine et surtout rodopréquine, qui associe pamaquine et rhodoquine) pour la cure radicale de cette maladie. Le traitement de routine adopté depuis 20 ans consiste à faire suivre le traitement d'attaque de l'accès palustre d'une cure de prémaline (association dans le même comprimé de chloroquine et de rodopréquine) sur le rythme hebdomadaire pendant 2 ou 3 mois et sur le rythme bimensuel pendant les 2 ou 3 mois suivants.

Cette méthode a été apliquée avec succès sur des milliers de cas de paludisme à *P. vivax,* si fréquents dans certains de nos territoires (Afrique du Nord en particulier).

Depuis l'introduction de la primaquine j'ai substitué cette nouvelle amino-8-quinoleine à ses prédécesseurs en traitant un nombre important de malades atteints par *P. vivax* avec (pour les adultes) l'administration hebdomadaire pendant 3 mois et bimensuelle pendant 2 autres mois d'une dose de 300 mg de chloroquine associée à 15 mg de primaquine. Le résultat de cet essai, comencé en 1952 et poursuivi jusqu'à ce jour, a été excellent, car jusqu'à présent je n'ai constaté aucune rechute sur les malades qui ont été régulièrement suivis.

L'association est parfaitement bien tolerée aussi bien par les adultes que par les enfants, pour qui les doses sont: 200 mg de chloroquine + + 10 mg de primaquine de 2 à 12 ans et 100 mg de chloroquine + 5 mg de primaquine au dessous de 5 ans.

Cette excellente tolérance a d'ailleurs été confirmée par des essais de chimioprophylaxie actuellement en cours dans le Nord-Cameroun, où nous administrons depuis plusieurs mois, une fois par semaine, les mêmes doses de médicaments.

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 239-241, 1959

Dr. GABALDON. *Comments on the relationship between malaria and nephritis* by Dr. GIGLIOLI — In Venezuela it has been observed in the last ten years a marked reduction in the rates of nephritis mortality. A study was made of the reduction of nephritis mortality in two areas: *a*) the five States with highest prevalence of malaria; and *b*) the five States with lowest malaria prevalence. As Table 1 shows, in both areas there was a similar reduction of nephritis mortality, what suggests that there was no relationship between malaria and nephritis.

TABLE 1 — *Venezuela: Malaria and nephritis mortality rates in two areas of different malaria prevalence*

Years	Area with high malaria		Area with low malaria	
	Malaria	Nephritis	Malaria	Nephritis
1941	361.4	51.7	13.7	62.3
1942	365.8	53.2	15.8	59.0
1943	262.0	40.5	15.5	57.2
1944	203.8	44.7	9.5	56.6
1945	156.5	42.8	9.1	54.5
1946	106.2	38.4	9.3	44.4
1947	62.4	45.1	3.1	43.0
1948	29.7	32.4	2.9	38.5
1949	22.5	27.8	1.5	33.8
1950	11.1	22.9	1.3	22.5
1951	5.4	18.4	1.1	25.7
1952	1.8	20.5	0.5	18.4
1953	0.5	22.4	0.4	20.4
1954	0.3	18.4	0.2	20.3
1955	0.5	—	0.2	—

On the other hand, it has been observed in Venezuela a great reduction in skin infections following the use of insecticides which have decreased the frequency of *Tunga penetrans, Sarcoptes scabiei,* and *Pediculus capitis*. Furthermore, with the increase in the standard of living there has been a wider use of soap which has also reduced skin infections and ulcers following small wounds. Also the introduction of the sulfa drugs and antibiotics has decreased the length of these infections.

It is believed that probably the eliminations of the skin lesions mentioned above, has been mostly responsible for the decrease in nephritis mortality in Venezuela.

Dr. R. S. Bray (U. K.) — Dr. Alving can you give us some idea of the maximum tolerated dose of primaquine as a single dose in primaquine-sensitive Africans and what high safe dosage would you recommend for mass monthly administration in Africa?

Dr. Alving (U. S. A.) — 45 milligrams of primaquine base per week I consider to be the maximum dose that may safely be given to adults who are sensitive to the hemolytic effect of primaquine. American adult negroes have an average weight of 150 lbs., but some may weigh as little as 90 lbs. We do not know the incidence of primaquine sensitivity in adults African negroes nor in children. For this reason we are not willing at this time to advise dosage schedules for field use.

Dr. Soerono (Indonésia) — In the execution of the malaria eradication program in Indonesia, we have to take in consideration the possibility that in some areas in conection with the circumstances it may not be possible to carry out the residual.

Then we have to find other ways to eradicate the malaria in those areas. One of these ways is the use of drugs mixed with salt.

The problem is that in our country the salt is not consumed in the form of table-salt, but together with the food (rice, vegetables, meat, fish, etc.) cooked in water or oil. It is therefore necessary to investigate first the attitude of the drug when exposed to high temperature.

An investigation was made with the following results. Cooked in *oil:* — temperature 250° C: 40 % of the drug is round
— temperature 300° C: 0 % of the drug is found
— the oil gets a brown colour.

No investigation was made in the toxicity of the newly formed product.

No investigations were made with chloroquine or other drugs.

It seems to me that it will not be possible for our country to use chloroquine mixed with salt in the malaria eradication program.

SECTION 3

EPIDEMIOLOGY AND PROBLEMS OF CONTROL

1st session: *Tuesday, September 9th, 3:00 to 4:30 p.m. Room D*

The meeting was held under the Cairmanship of Dr. George MacDonald and Dr. H. T. Soeparmo.

The Rapporteur was Dr. O. Mastbaum and the Secretary was Dr. Jorge Melo Vieira.

The following papers were presented and discussed:

PROGRESS OF EPIDEMIOLOGY AND CONTROL OF MALARIA

O. Mastbaum — Swaziland

A summary of recent progress in the field of malaria control and epidemiology had to be curtailed to the time at my disposal and it is impossible to give a detailed account of all the work being done and published within the last 5 years. I have, therefore, to apologize to many authors if their work, although important is omitted from this summary.

The fight against malaria has in recent years become a world wide campaign and the number of successful projects with the final aim of total eradication are becoming more numerous every year. It is only right to say that these successes have been made possible by the great impetus the work has received by the interest and active support international agencies like WHO, UNICEF and many more have given to countries whose own resources were insufficient to undertake territory wide campaigns.

At this stage it may be of interest to recall P. Russels' analysis of the present malaria position in the world and, although the figures he published in 1956 may be somewhat higher now than at that stage, they give a good illustration. Of approximately 1070 million people living in malarious areas 375 million, or 35 %, are now protected. There is a great variation from continent to continet and while many countries have achieved either a total or an over 50 % protection of their people others are still far behind, especially East — Central and West Africa, Oceania and Australia. From these figures it is clear that, although big strides have been made in recent years, there still remains an exceedingly large task requiring both research and action. It deserves, however, to be mentioned that many countries like North America, Italy including Sardinia and Sicily, Corsica, Cyprus, British and French Guiana — to name only a few — have already succeeded in total eradication; many more are well on the way to this final goal, including some parts of «Dark Africa» like Mauritius, Reunion, Transvaal and Swaziland.

The problems of malaria and the control of it are (as you know) different from country to country and only intricate knowledge of local epidemiology will safeguard success of control. I think no greater contribution to this knowledge has been made than that by our chairman, Professor Macdonald and his school, whose concept of epidemiology and control has given a guide to tackle and to solve the many problems malariologists and entomologists are facing in every part of the world. Even if not all of us — myself included — can follow him in his mathematical approach to the end, we still can find the necessary guidance in his standard work.

And if we follow the lines laid down by him in the investigation of pre-control, control and after-control surveys, we will attain a complete picture of the epidemiology of malaria and, probably equally important, results published in different parts of the world will be comparable.

ECOLOGY OF VECTORS

The work on the ecology of different vectors throughout the world has been advanced greatly in recent years and many gaps in our knowledge have been closed. Publications on the subject are numerous, most of them of local interest, but some of general importance deserve to be mentioned. M. T. Gillies and Davisons' work in East Africa on the age composition and exophily of the main African vectors has contributed a great deal to the understanding of vector biology. The technique of examination of the mating plug, the measurement of ampullae and the immediate and delayed sporozoites rates described by Davidson and Draper have become a useful weapon ascertaining the longevity of mosquitoes, an information necessary for the computation of reproduction rate. Equally important are the observations of Hamon and Mouchet in French African territories. The question whether exophily of a vector has an important bearing on the success of imagicidal control has been investigated and generally speaking one can conclude that exophily in itself will not necessarily interfere with imagicidal control.

This has recently also been confirmed by Ronnefeldts' observation in Columbia with *A. punctimaculata*. The study of anthropophylic and zoophylic behaviour of a vector, which naturally has an important bearing on the inoculation rate, has been made possible on a wide scale by the assistance of Dr. Weitz of the Lister Institute to malariologists and entomologists all over the world. The importance of a change in vector behaviour during or after imagicidal control may tend to explain some epidemiological problems. This was recently demonstrated by Dr. Hoslstein and his team in Swaziland, where the previously highly anthropophylic *A. gambiae* was found to feed now almost exclusively on cattle.

This change in behaviour may be the reason why we were unable to demonstrate secondary cases from an occasional — usual imported — primary case in our territory. Whether this change is a permanent and stable feature — I hope it is — or whether it is transient and reversible, only time can tell. It is of interest that a similar observation has recently been published by Halcron from Mauritius.

Special mention should be made on M. Holsteins' work on cytogenetics of *A. gambiae* and, although no conclusive results have been obtained, the morphological differences in chromosomes may throw some light on resistant or susceptible strains, or generally, on different races of a vector.

The relationship of gametocyte (crescent) densities and infectivity has been investigated by Muirhead Thomson in Ghana and in a Liberian village. His approach to the problem of exposing large batches of laboratory bred *A. gambiae* to children and adults in a hyperendemic area and observe later the percentage of infected anophelines is interesting. Of particular importance are his observations that even very low gametocyte densities may infect a mosquito while on the other hand high densities are not always capable of doing so. This has some significance in assessing the part the immune adult group is playing in transmission. Seasonal variations on the production of gametocytes has again been described by Professor Morin.

As the presence and density of gametocytes in the peripheral blood is influenced by the degree of immunity, it may be opportune to say just one word of immunity in relation to effective control. Previous concept of immunity would lead to believ that malaria control in an endemic or hyper-endemic area would greatly reduce the existing degree of immunity in the population. Belios reported recently from Greece that after many years of successful control a strong immunity was still present in the population against *P. vivax*. We have made a similar observation in Swaziland with *P. falciparum* and although the evidence is not conclusive on account of limited observations, low parasitaemias with very scanty production of gametocytes and the absence of clinical manifestations is the rule rather than the exception in the few Swazi — adults and older children, who have acquired an infection outside the country. One wonders, if immunity, once acquired, is not a much more stable condition than hitherto believed. It would be interesting to hear some more observations and experience on this rather important question.

RESISTANCE

Since first anopheline vector resistance to chlorinated hydrocarbons was reported by Professor Livadas from Greece in 1951 this important and menacing occurrence has been reported from many parts of the world in different vectors. Investigations into the presence of resistance were greatly facilitated by the comprehensive studies of Busvine who developed the new familiar techniques of testing laboratory bred and wild mosquitoes. With the assistance of WHO these tests can now be done everywhere in the field. Fortunately a vector resistant to one group of hydrocarbons is usually still susceptible to the other group with the probable exception of *A. sacharovi*. Resistance has now been found and confirmed in the following vectors:

A. sundaicus from Burma and Indonesia

A. gambiae from Nigeria, Liberia, Haute Volta & French West Africa

A. maculipennis

A. sacharovi from Greece and Lebanon.

A. superpictus
A. stephensi from Iraq and Iran.
A. subpictus from Java
A. quadrimaculatus from America.

It is of great interest that the same vector as for instance *A. gambiae* may quickly develop resistance in one part of Africa while in other parts even after exposure of may years to residual insecticides no such resistance has ever been observed. Davidsons' work of separating resistant, hybrids and susceptibles in wild caught mosquitoes by fractional dosage of insecticides is of particular interest. Although a great deal of work has already been done there remains still ample room for further intensified research on this vitally important question.

INSECTICIDES

A wealth of information with regard to formulation, dosage, absorption and sorption and influence of climatic factors on the residual effect of insecticides are now at our disposal. The choice of an insecticide to be used depends on local conditions which have to be accurately assessed leave out before the commencement of imagicidal control. Every malaria control project to be undertaken will have the benefit of the investigations done by Barlow and Hadaway and by Burnett and Davidson and many others. Analysis and estimation of insecticides after application can be done rapidly and accurately by the Allessandrini or other tests and have proved a great aid in the study of the residual effect of a respective insecticide. There is, of course, still much room for further research on improvement of existing insecticides and the development of new ones.

CONTROL

In the present state of our knowledge of control, vector eradication is not a general possibility and fortunately not a necessity. Vector eradication although achieved in some instances can not be attained by imagicidal control. Although it should not be forgotten that there are examples where eradication of the vector has been achieved, as for instance in Brazil and Egypt by larvicidal methods against invading *A. gambiae* or by imagicidal control against *A. darlingi* in some parts of South America, noticeably in British Guiana, and possibly against *A. funestus* in Mauritius and some localised places of the Belgian Congo and Madagascar. But apart from these few instances, which were probably possible through an exceptionally high endophily and accordingly high mortality of the vector, eradication of malaria vectors are generally not attained by imagicidal control. Nevertheless malaria control and its logical final aim of eradication has been impressively successful in almost every part of the world within the last 5 years. The documentation of this work has grown to such an extent that it is not possible to mention the progress in detail. Interruption of transmission, the first step in an eradication program, has been achieved with one or the other insecticide under widely different epidemiological conditions. Recognised malaria vectors, numbering almost 50 throughout the world, have yielded to well planned insecticidal campaigns almost everywhere. The only exception to this happy state of affairs seems to be some parts of Tropical Africa where in spite of sometimes prolonged spraying interruption of transmission could not be achieved.

During a recent technical conference convened by WHO in Brazzaville the reason for the failures and probable ways of improving the efficiency of the measures employed were discussed. There is no doubt that in Equatorial Africa, which has probably the highest endemicities known in the world, the problems of malaria control are formidable. These problems are not only connected with the ecology of the vectors, but many difficulties, not met elsewhere, which can be summarised as administrational, technical and environmental, have to be overcome. Imagicidal control necessary for the interruption of transmission in these regions must probably achieve a daily vector mortality of the order of 65 % and more and even with an organisation of extremely high standard of efficiency this cannot easily be attained. But in spite of the many setbacks of malaria control in tropical Africa there is hope that in case house spraying with residual insecticides alone will not succeed in complete interruption of transmission a combination of insecticidal control with an auxiliary measure such as mass-treatment of the population with antimalarial drugs will finally produce the desired effect.

CHEMO-PROPHYLAXIS IN RELATION TO MALARIA ERADICATION

A great deal of work on mass treatment with anti-malarial drugs has already been done. The drugs mainly used are Chloroquine, Amodiaquine, Pyrimethamine or a combination of both. The ingenious method introduced by Pinotti in Brazil by incorporating Choroquine in a universally used foodstuff such as salt in the control of malaria of primitive inaccessible tribes in the Amazone valley deserves foremost mentioning. However, this very attractive way of drug prophylaxis is probably not generally attainable as the salt is usually supplied from many sources, especially in most parts of Africa, and the supply by a single source would rouse suspicion and mistrust of the local people. Further, infants and young children would probably not get the treated salt due to the late age of which lactation is continued in many parts of Africa. However, it would be worthwhile to investigate further under which conditions Pinottis' method could be used in different parts of the world.

Farinaud and Choumara have reported good results in mass prophylaxis with Chloroquine but they were disappointed with the use of Pyrimethamine in Indochina. Effective mass-prophylaxis with Pyrimethamine has been reported by Vincke and his team from the Belgian Congo. Experiments with the same drug were carried out by Bruce--Chwatt, Archibald and Charles in Nigeria and by Miller in Liberia. Encouraging results were achieved in Senegal and Gambia using either a combination of Chloroquine and Pyrimethamine or Daraprim alone. However, the results of these and other similar experiments are somewhat conflicting and there appears to be still soon for further research with special emphasis on the following problems:

1) Dosage and interval of drug administration.

2) The advisability and necessity of combined insecticidal and chemo-therapeutical control under different epidemiological and environmental conditions.

3) The value of single dose treatment in the course of spraying operations.

4) Choice of drug or combination of drugs with special reference to their schizonticidal and sporontocidal effect. In addition the technique of drug administration to groups of mostly primitive people deserves

the closest attention as this is in my experience one of the major obstacles in the success of chemo-prophylaxis amongst a rural population.

Up to the present time drug resistant strains of parasites have not caused major concern, although drug resistance mainly against Pyrimethamine is known and has been reported by Clyde and co-workers from a costal region in Tanganyika, but apparently not from other places of the same territory. It may also have occurred in West Africa, but the evidence is not conclusive. It appears that resistance, if present, may be confined to localised foci. Nevertheless, the fact has to be kept in mind and has to be investigated wherever chemo-prophylaxis is planned on a large scale.

Although this summary had to be kept brief and rather sketchy it conveys the big strides which have been made in our knowledge of epidemiology and control of malaria in recent years. But, one also realises that many obstacles are still in our way which have to be overcome by continued research and action before we have reached our final goal of world wide malaria eradication. From my own experience of many years of pratical work in Africa I have little doubt that this goal can be attained in the not too far distant future.

NOVOS CONCEITOS NA CLASSIFICAÇÃO DE ENDEMICIDADE MALÁRICA (¹)

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Dentro dos conceitos clássicos de epidemiologia, a malária pode ter um dos seguintes tipos de ocorrência em função da sua incidência: esporádica, endémica e epidémica. A malária é *esporádica* quando os casos autóctones são em número tão reduzido e de distribuição tão esparsa que não causa qualquer efeito mensurável na comunidade. É *endêmica* quando a sua presença é constante por vários anos seguidos, podendo medir-se a sua incidência todos os anos pelo efeito causado na comunidade. A malária diz-se *epidémica* quando ocorre um número significativamente grande de casos autóctones em um espaço de tempo relativamente curto, em área anteriormente sem malária (surto epidémico = = *epidemic outbreak*) ou com malária geralmente de baixa endemicidade (exacerbação epidémica ocasional = *occasional epidemic exacerbation*).

Nas áreas de malária endémica há transmissão durante anos sucessivos, transmissão que pode ocorrer durante apenas certo período do ano (malária estacional = *seasonal malaria*) ou durante todo o ano, com menor ou maior recrudescimento estacional (= *seasonal rise*); este recrudescimento pode ser anualmente baixo ou moderado e quinquenal ou paraquinquenalmente alto. Há quem considere esses recrudescimentos estacionais como epidemias (= *seasonal epidemics*), classificando-os em pequenas epidemias estacionais (= *minor seasonal epidemics*), quando baixos ou moderados, e grandes epidemias estacionais (= *major seasonal epidemics*), quando altos na periodicidade quinquenal ou paraquinque-

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(¹) Apresentado aos VI Congressos Internacionais de Medicina Tropical e Paludismo, Lisboa, Portugal, 5-13 de Setembro de 1958, como trabalho de co-relator da Secção 3, Epidemiologia e Contrôle, Divisão B, Paludismo.

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 250-258, 1959

nal; para os que assim pensam, um quarto tipo de ocorrência deve ser constituído, a malária *endemoepidémica*. Covell, Russell e Swellengrebel (1953), no entanto, no seu relatório *Malaria Terminology* para a Organização Mundial de Saúde, não admitem o emprego do termo epidemia para os recrudescimentos estacionais.

A malária esporádica, expressão mínima de uma malária endémica, mais comummente, ou epidémica, mais raramente, não deve ser considerada como um tipo especial de ocorrência de malária; melhor será denominá-la subendémica. Por outro lado, tivesse a malária endemoepidémica justificativas maiores para se constituir em tipo de ocorrência, seria, como o seu próprio nome indica, a resultante da superposição de uma condição epidémica a uma situação endémica. Assim, são realmente tipos básicos de ocorrência a malária endémica e a malária epidémica, cujos efeitos numa comunidade exposta podem ser grosseira e geralmente esquematizados:

1. *Malária endémica* — Índice esplénico alto ou baixo, conforme o grau de endemicidade, podendo ser mais alto nas crianças que nos adultos, tendência que se acentua com o maior grau de endemicidade. Esplenomegalia média moderada ou alta. Grandes esplenomegalias relativamente frequentes. Tendência a maiores índices parasitários, densidade parasitária e gametocitemia entre as crianças, segundo o maior grau de endemicidade. Infecções mistas comuns.
2. *Malária epidémica* — Índice esplénico alto ou baixo, conforme a intensidade da epidemia, sem maior diferença entre crianças e adultos. Esplenomegalia média baixa. Grandes esplenomegalias raras. Índice parasitário, densidade parasitária e gametocitemia tão altos em crianças como em adultos. Infecções mistas raras.

Pela análise de dados malariométricos relativos ao homem infectado (baço e parasita), pode, pois, chegar-se a uma conclusão sobre o tipo de ocorrência da malária numa comunidade. Essa conclusão, porém, nem sempre é satisfatória, principalmente se baseada em um único inquérito ou em um só ano de observação, tendo em vista a variabilidade de incidência da malária. Comummente, na prática, conforme o grau de endemicidade e de epidemicidade, encontram-se quadros de difícil, se não impossível, interpertação, impondo-se a comparação com dados semelhantes de anos anteriores para que se chegue a uma conclusão certa sobre o tipo de ocorrência da malária.

Embora Wilson e Wilson (1937) tenham apontado o índice parasitário nas crianças como o mais acurado índice de endemicidade, já empregado por Stephens e Cristophers desde 1902, para comparações e mapeamento de malária endémica, e Barber, Rice e Mandekcs (1936) demonstrassem o seu valor em menores de 1 ano de idade como índice de transmissão numa comunidade, as esplenomegalias, cuja importância na epidemiologia da malária foi pela primeira vez registada por Dempster (1848), vem constituindo-se, tradicionalmente, desde Ross (1908), no elemento de medida da endemicidade malárica. Esta avaliação vem sendo feita pelo índice esplénico e pela esplenomegalia média (baço médio aumentado), isolada ou associadamente (= índice esplenométrico). A associação dos índices parasitário e esplénico também tem sido utilizada como índice de endemicidade, tais como o índice endémico de Ross (1910) e o índice de Macdonald (1931); a comparação entre eles também já foi empregada na avaliação do grau de endemicidade.

Mas a medida de endemicidade mais comummente usada tem sido mesmo o índice esplénico, ainda que reconhecidas as influências que pode sofrer das esplenomegalias produzidas por outras doenças e as variações de tamanho normal e de reacção do baço à infecção palúdica, variações individuais, etárias, raciais e regionais que, sem dúvida, podem distorcer o valor do índice esplénico. Um dos últimos trabalhos sobre estas variações (Bruce-Chwatt, 1956) mostra que o peso do baço de africanos é bem maior que o de europeus (1,5 a 2 vezes maior) e que entre os primeiros o baço precisa aumentar de 2,5 e 1,6 vezes o seu peso, e provàvelmente o seu volume, para se tornar palpável em adultos e crianças, respectivamente.

Baseadas no índice esplénico, várias classificações do grau de endemicidade malárica foram seguidas. A última, proposta pela O. M. S., na Primeira Conferência de Malária da África Equatorial, realizada em Kampala, Uganda, em 1950, classifica a malária em hipoendémica, mesoendémica, hiperendémica e holoendémica, conforme o índice esplénico em crianças de 2-9 anos seja, respectivamente, inferior a 10 %, de 11 a 50 %, constantemente superior a 50 % e alto nos adultos e constantemente superior a 75 % e baixo nos adultos. Largamente adoptada, esta classificação, organizada especìficamente para a África, onde vem sendo satisfatòriamente aplicada, nem sempre se coaduna a regiões de outros continentes, não traduzindo fielmente a sua situação malárica. Para citar um único exemplo: na Nova Guiné, áreas reconhecidamente de malária holoendémica seriam confundidas, pela classificação da O. M. S., com áreas de malária hiperendémica, já que o índice esplénico entre os adultos não é baixo, sendo tão alto quanto o das crianças. Contudo, essa classificação apresenta uma melhoria em relação às anteriores: o «constantemente» superior a 50 e 75 % para a caracterização dos dois últimos graus de endemicidade. Como é sabido, o índice esplénico mede a malária presente; assim, pode ter-se um mesmo índice esplénico em plena endemia e em plena epidemia, traduzindo a mesma quantidade de malária, sem, no entanto, expressar a ocorrência endémica ou epidémica. Para isto, seria necessário ter-se o índice esplénico da comunidade durante algum tempo, alguns anos, a fim de, conforme a sua variabilidade, concluir-se por endemicidade ou epidemicidade. A palavra «constantemente» na classificação da O. M. S. faz pressupor o levantamento do índice esplénico durante esse tempo.

Gabaldon (1946), reconhecendo as dificuldades e as deficiências das classificações desse tipo, cria o que chama de *razão de endemicidade* e *razão de epidemicidade,* traduzindo numèricamente o que denomina de *constituição da malária* (1949) numa comunidade e representando ainda a base do índice esplénico, a quantidade e a variabilidade da doença, ou seja, respectivamente, a sua endemicidade e sua epidemicidade. Considerando que o índice esplénico mede a quantidade de malária presente, que esse índice levantado anualmente indica a quantidade de malária presente em cada ano, isto é, a sua variação anual, que 5 % pode ser considerado como um índice normal, possível de ser encontrado entre as crianças de uma área não malarígena e que a malária tem certa tendência a uma periodicidade quinquenal ou paraquinquenal, calcula as suas razões:

Razão de endemicidade: dividindo o menor índice esplénico num período de 5-7 anos por 5.

Razão de epidemicidade: dividindo o maior pelo menor índice esplénico no período de 5-7 anos (quando o menor índice esplénico é inferior a 5 %, o divisor é 5).

A primeira mede a prevalência mínima da malária, sua endemicidade, a segunda o máximo de variabilidade da malária, sua epidemicidade. Dentro desse conceito, Gabaldon (1956) apresenta uma série de localidades malarígenas da Venezuela dividida em três grupos, conforme a sua *constituição malárica*: 1.°) com alta endemicidade e baixa epidemicidade; 2.°) com baixa endemicidade e baixa epidemicidade; e 3.°) com baixa endemicidade e alta epidemicidade. Estas constituições correspondem, respectivamente, a 1.ª) grande prevalência da malária durante anos seguidos e, consequentemente, pequena variabilidade anual; 2.ª) pequena prevalência e pequena variabilidade anuais; e 3.ª) pequena prevalência em alguns anos e grande em outros, havendo, pois, grande variabilidade. Classifica, ainda, os graus de endemicidade e de epidemicidade: ALTA ENDEMICIDADE = razão 10 para cima, BAIXA ENDEMICIDADE = razão 3 para baixo, ALTA EPIDEMICIDADE = = razão 5 para cima, e BAIXA EPIDEMICIDADE = razão 3 para baixo. Valores intermediários, lògicamente, podem ser encontrados, indicando constituições maláricas intermediárias aos três tipos considerados.

Esse mesmo conceito de endemicidade e de epidemicidade pode ser traduzido em função da taxa de mortalidade por malária, ou por «febres» quando houver insuficiência de registo. Num período de 15 anos escolhem-se as cinco menores taxas de mortalidade, calculando-se a sua média aritmética; se esta for muito baixa, a endemicidade é baixa, ainda que tenham ocorrido epidemias durante o período em questão, e, se for relativamente alta, a endemicidade é alta. Estabelece-se, assim, um índice de endemicidade, que foi seguido no México para a delimitação das áreas de malária endémica (Swaroop, 1957). Comparando-se as taxas máxima e mínima, tem-se um índice de epidemicidade, como vem sendo levantado no Punjab (Macdonald, 1957). Para o cálculo destes índices, como das razões de Gabaldon, necessitam-se, pois, de dados de vários anos, nem sempre, porém, disponíveis.

Macdonald, numa série de trabalhos (1950, 1952, 1953), condensados no seu livro *The Epidemiology and Control of Malaria* (1957), estuda e analisa a epidemiologia da malária em termos matemáticos, sugerindo a classificação primária da sua ocorrência em dois tipos: *malária estável* e *malária instável*, na base do comportamento e das características do vector ou da natureza epidemiológica observada, e à qual todas as outras classificações seriam subordinadas ou subsidiárias. Para ele, a ocorrência da malária no mundo pode ser representada por um vasto e fluido espectro, uma contínua série de gradações, cujos extremos são ocupados por aqueles dois tipos. Essa classificação é feita, não em função dos efeitos da malária na comunidade (índice esplénico, índice parasitário, mortalidade, etc.), como as anteriores, mas em função dos hábitos do vector, propondo como escala o número de picadas no homem do mosquito transmissor durante a sua vida nrmal, que constitui o que chama de *índice de estabilidade*. Quanto maior esse número, este índice, tanto maior a estabilidade da malária. Admitindo que esse número possa variar na natureza, entre as espécies vectoras conhecidas, de um máximo de 10 a um mínimo de 0,1 ou menos, propõe Macdonald a seguinte classificação empírica:

1. Índice de estabilidade abaixo de 0,5 = malária instável.
2. Índice de estabilidade entre 0,5 e 2,5 = malária de média estabilidade.
3. Índice de estabilidade acima de 2,5 = malária estável.

Anofelinos com alto grau de antropofilia e grande longevidade geram malária estável; com baixo grau de antropofilia e pequena longevidade, malária instável; com alta antropofilia e pequena longevidade ou vice-versa, malária de tipo intermediário.

Dentro desse conceito de Macdonald, o que deve presidir à classificação da malária é a sua variabilidade/estabilidade, e não pròpriamente a sua endemicidade, comummente empregada como sinónimo de quantidade. Assim é que malária em alta endemicidade pode ocorrer onde a sua constituição é instável (Ceilão), como onde a sua constituição é estável (África Equatorial). No Ceilão, no entanto, ocorrem epidemias, acentuadas flutuações na incidência da malária, e na África Equatorial a malária se caracteriza pela ausência de epidemias, por oscilações muito pequenas em sua ocorrência.

Embora as medidas usadas sejam diferentes, parece-nos que o conceito de Macdonald é muito comparável ao de Gabaldon. A determinação do grau de estabilidade ou instabilidade daquele é feita pelos hábitos do mosquito transmissor e a razão de endemicidade ou epidemicidade deste pelos efeitos da malária na comunidade; o primeiro usa o número de picadas do vector, o segundo o índice esplénico. Mas à malária estável de Macdonald corresponde a malária de baixa epidemicidade de Gabaldon e à malária instável daquele a de alta epidemicidade deste. Para o levantamento do índice de estabilidade de Macdonald não se necessitam de dados pregressos, mas são indispensáveis conhecimentos acurados sobre a antropofilia, a longevidade e a frequência de alimentação do vector, nem sempre fàcilmente conseguidos; para o levantamento das razões de Gabaldon necessitam-se de dados pregressos, mas são dispensados conhecimentos sobre aqueles aspectos da biologia do transmissor.

A classificação do tipo de ocorrência e da quantidade de malária numa comunidade sempre constituiu preocupação dos malariologistas, que, assim, poderiam sintetizar os aspectos epidemiológicos da malária, compará-la em várias regiões, estimar a viabilidade do seu combate e avaliar os progressos deste. Hoje, porém, comprovada a possibilidade de erradicação da malária, tal preocupação passou a ser secundária.

Realmente, hoje é geralmente aceite, diante dos resultados obtidos em alguns países, que com o emprego bem indicado e bem conduzido de insecticidas de efeito residual, interrompendo a transmissão da malária numa região por um período de 3-4 anos, consegue-se a erradicação da doença por um esgotamento natural das fontes de infecção. Assim, a preocupação maior do malariologista é erradicar a malária; transformando programas de *contrôle* em programas de erradicação e procurando desenvolvê-los o mais prontamente possível, tendo em vista o fantasma, em algumas áreas já materializado, da aquisição de resistência dos anofelinos aos insecticidas. Num programa de *contrôle,* quando se procura reduzir a malária a uma prevalência mínima, a classificação do seu grau de endemicidade tem a sua razão de ser, pois a sua redução traduz a eficácia dos métodos em uso, o quanto foi feito de útil. Num programa de erradicação, no entanto, cujo objectivo é eliminar a malária e, consequentemente, atingir o *zero,* a classificação do seu grau de endemicidade é questão secundária. Num programa de *contrôle* é realmente importante saber-se — mesmo em números relativos, como são os índices — quanto existe de malária e como esta ocorre, antes do seu início e durante o seu desenvolvimento, para se poder avaliar os progressos alcançados; num gráfico que represente a marcha desse programa, as comparações são feitas com os valores à esquerda. Num programa de erradicação pouco interessa saber o *quantum* inicial de malária, só importando números absolutos que indiquem o que falta para se chegar a zero; no gráfico representativo da progressão desse programa as comparações são feitas com os valores à direita. Um programa de erradicação desenvolve-se em função de um único número — zero — e, assim, um, dez, cem, mil ou mais casos de malária têm, pràticamente, a mesma significação. Mas é indispensável saber-se, no decorrer do programa, se existem esses um, dez, cem, mil ou mais casos, o que deve ser feito por um registo o mais perfeito de morbilidade, através de um serviço minucioso e eficiente de busca desses casos. Desde que haja um só caso de malária, um programa de erradicação não está completo, não está terminado. A significação desse único caso numa comunidade pode ser bem avaliada pelo chamado *índice de reprodução* de Macdonald (1952), que representa, matemàticamente, o número de casos de malária que podem ocorrer numa comunidade, directamente originários de um único caso primário não-imune. Este índice, na dependência de vários factores, tais como espécies do parasita, densidade, antropofilia e longevidade do vector, temperatura ambiente, imunidade da população exposta, etc., pode chegar a 3000 e, até mesmo, 5000!

Num programa de erradicação, portanto na sua fase de desenvolvimento e principalmente na sua fase final, não interessam números relativos que expressem o grau de endemicidade ou de epidemicidade da malária, dados que traduzam a sua estabilidade ou instabilidade. Interessam, sim, números absolutos de morbilidade por malária, para que se saiba quanto falta para se chegar a zero e para se ter comprovação de que este objectivo foi alcançado.

Assim, embora de certa utilidade no planejamento das campanhas, as classificações de tipos de ocorrência e de endemicidade malárica parecem-nos totalmente superadas nesta época em que a tendência geral dos malariologistas é pensar em termos de erradicação da malária, o ideal sempre perseguido e só ùltimamente vislumbrado.

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CLASSIFICATION OF MALARIA

D. Metselaar and P. H. van Thiel (Neth. New Guinea and Leyden)

In a classification of malaria, based on a number of mosquito characteristics and on the duration of the extrinsic cycle, Macdonald (1952) distinguishes «stable» and «unstable» malaria as the ends of a continuous range of levels at which parasite rates or other indices of the proportion of people affected, has come to equilibrium at the end of periods of change. This classification appears to be a good primary one, because it integrates in a transparent way the various factors which have a bearing on malaria epidemiology.

We feel, however, that, everywhere in malarious countries, in the daily practice of the malariologist, there is still need of the possibility to classify malaria according to the results of one or two simple surveys performed on population groups. Gabaldon's (1949) cannot serve as such. The classification of the Kampala Conference (WHO, 1951), based on the course of the spleen rate in relation to age, might be seen as an expression of this need for simplicity. It assumes that the course of the spleen rate age curve is determined by the frequency of infections to which populations are exposed and by the degree of immunity developed by these populations in response to that number of infections. It assumes also that the response of the spleen rate to immunity is always and everywhere the same.

According to this classification, malaria is labelled hypoendemic, mesoendemic, hyperendemic or holoendemic when the spleen rate in children aged 2-10 years is successively: under 10 %, between 11 % and 50 %, over 50 % and over 75 %. Besides, the spleen rate in adults must be high in hyperendemic, but, supposedly as a result of the very high degree of immunity, low in holoendemic malaria. Moreover, holoendemic malaria is supposed to be accompanied by an absolute parasite rate approaching 100 % early in the second year of life and subsequently declining throughout life, while the parasite density declines rapidly between the second and fifth year and then more slowly.

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One of us (Metselaar, 1956, 1957) studied stable malaria in the Nimboran Valley in Netherlands New Guinea. The absolute parasite rate agreed very well with that of holoendemic malaria (Kampala classification). The parasite counts were relatively low, but not in disagreement with the characteristics of holoendemicity. The number of infections to which, according to entomological observations, the population was exposed, amounted to 150 or more per adult, well divided over the year. This, too, is well within the definition of holoendemicity (Wilson, 1936; Wilson *et al.*, 1950). Only the spleen rate runned a deviating course. Though approaching 100 % at the age of 1 year, it remained at 78 % in adults over 24 years of age.

Moreover, observations on Papuan schoolboys, aged 13-19 years, who took suppressive drugs for 15 months without significant fall of their spleen rate, and (unpublished) observations in another holoendemic area in New Guinea where the spleen rate of adults and older children 4 years after insecticide spraying showed only a moderate fall notwithstanding considerable inprovement of the parasite rates, almost compel one to the conclusion that Papuan spleens do not readily retract below the costal margin, once they have been enlarged for some years by malaria.

In two Indian tribes living near each other and exposed to the same high risks of malaria infections, Viswanathan (1951) observed that in the tribe living for centuries in the area, the spleen rate in adults went down considerably, but in the other tribe, which had been living in the region for a limited number of generations only, the adult spleen rate remained high. According to Viswanathan, this difference, together with a difference in parasite counts, could be explained by a natural selective tendency towards a very high degree of tolerance, which has developed in the oldest tribe. This high degree of tolerance should result in high parasite counts in infants and a low spleen rate in adults. For this condition Viswanathan proposed the name «superendemicity». Otherwise he follows mainly the Kampala classification.

It seems not improbable that such a selection is possible. However, this needs not imply that adult spleen rates necessarily go down wherever such high racial tolerance has been obtained. If the theory was generally applicable, Papuans of New Guinea should not have obtained the highest degree of tolerance so far observed. However, there are indications of such a high tolerance in Papuans as well. Mackerras & Sandars (1954) observed an epidemic of malign tertian malaria with strikingly light symptoms in the previously almost malaria-free Torres Straits Islands, south of New Guinea. Metselaar (*op. cit.*) observed, besides relatively little suffering in infants in the holoendemic Nimboran, an astonishing rarity of severe illness of inhabitants of mesoendemic islands in Sentani Lake.

Other explanations than «survival of the fittest» might, therefore, serve as well as an explanation for the discrepancy in adult spleen rates in otherwise comparable highly endemic areas. Metselaar (*op. cit.*) points to sicklecell anaemia as a possible cause of low adult spleen rates. This phenomenon occurs in high percentages both in the oldest tribes of India (Lehman & Cutbush, 1952) and in negros. Allison (1956) relates these high frequencies to «survival of the sicklers» as a result of the protection which haemoglobin S affords against malaria. It seems not unreasonable to expect that, once immunity is well established in individuals and spleens become smaller, the seize of spleens in sicklers will be reduced more than that in non-sicklers. In this way sicklers could contribute to a lower spleen rate in adults.

Spleen rates might be influenced also by nutrition, by different prevalence of species of parasites, or by differences of pathò-geographical origin not yet understood.

May on the one hand the Kampala classification cause confusion when applying its standards of holoendemicity to regions of comparable malaria risks, these standards can, on the other hand, rightly be applied to spleen rates found in some islands east of New Guinea, but where conditions differ radically from those in classical holoendemic regions (Black, 1954). It may, therefore, be concluded that the spleen rate is not a useful yeardstick for classification of malaria.

This is not suprising. Basic factors which determine the degree of malaria are the number of infections to which a population is exposed, and their distribution over the year. These factors determine the ultimate immunity, the stability or unstability, and whether malaria is seasonal or perennial. Logically this number of infections finds its immediate reflection in parasite rates and parasite counts. But even this reflection needs not always be the same in different populations and may vary with the state of nutrition, the species of parasite prevalent, the presence of abnormal haemoglobins, or race-bound immunity. It is to be expected that the spleen rate, which is secondary to parasitaemia, and which itself, for the reasons mentioned, may vary in its reactions to the parasite rate, shows even more variations.

From the point of view of malaria control it is the infection risk which is of utmost importance. The higher it is, the more difficult control. It seems logical, therefore, to look for a classification in which this risk is best reflected. From the foregoing it follows that the parasite rate should be considered first. It is less simple to handle than the spleen rate, but more accurate. The spleen rate, of less value for comparison of malaria conditions on a world-wide scale, is useful for this purpose more locally, and for the determination of the phase of an epidemic. In many regions also for a quick evaluation of the results of control measures.

The following classification is proposed, based on the absolute parasite rate, and for which much was borrowed from Kampla.

Malaria is:

Hypoendemic if the absolute parasite rate in the age-group 2-10 years is, as a rule, under 10 %. It may be higher part of the year.

Mesoendemic if the absolute parasite rate in this age-group is, as a rule, between 11 % and 50 %. It may be higher part of the year.

Hyperendemic if the absolute parasite rate in this age-group is constantly over 50 %.

Holoendemic if the absolute parasite rate is constantly over 75 % in the 1 year age-group.

In the first two groups the spleen rate may be higher or lower than the absolute parasite rate, according to the season. In hyperendemic malaria the spleen rate will, as a rule, be higher than the absolute parasite rate. In holoendemic malaria, the spleen rate in adults may be high (New Guinea type) or low (African type); the parasite density declines rapidly between the second and fifth year of life, and then more slowly.

Hypo- and mesoendemic malaria can be regarded as unstable. In hyperendemic malaria variations may occur, however, without severe epidemics. Holoendemic malaria is certainly stable.

It is thought that it will usually be possible to classify malaria, after one or two population surveys, in one of the groups described above. Difficulties will remain. But it will always be difficult to press biological happenings in a water-tight classification system.

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RESULTADOS DA CAMPANHA ANTIMALÁRICA NA REGIÃO DE LOURENÇO MARQUES APÓS 6 ANOS DE UTILIZAÇÃO DE UM INSECTICIDA DE EFEITO RESIDUAL (B. H. C.) COM ESPECIAL REFERÊNCIA AO SEU EFEITO SOBRE OS VÁRIOS SECTORES DA POPULAÇÃO DE LOURENÇO MARQUES

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A cidade de Lourenço Marques está situada no extremo sul da província de de Moçambique, a 25° 58′ de latitude S e 32° 35′ de longitude E.

A superfície da cidade é de 932 ha, mas, incluindo os bairros suburbanos, esta área é de 5346 ha.

Para defender a cidade contra a malária, estabelecemos duas linhas de defesa, a primeira constituída por uma zona suburbana avaliada em 4414 ha, que é constituída em grande parte pelos bairros predominantemente africanos, a segunda linha é constituída por uma larga zona sub-rural, formada por terrenos do tipo savana e bastante arenosos, que se estende num raio aproximadamente de 20 km para fora dos limites da cidade, e avaliada em 25 000 ha.

É nestas duas zonas que realizámos a nossa campanha imagocida, e o objectivo deste trabalho é avaliar, ao fim de 6 anos, qual o seu efeito sobre as condições de malária nesta vasta área urbana, suburbana e semi-rural (30 346 ha na totalidade).

A) CLIMA.

O clima é do tipo subtropical, ou seja temperado-quente, com predominância de chuvas na estação quente (Outubro-Abril). 80 % das chuvas caem neste período do ano.

A temperatura média anual é de 20,7° C, com uma variação térmica anual (diferença entre as temperaturas do mês mais quente e do

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 264-280, 1959

mês mais frio) de 7,3°. A temperatura mínima no decorrer do ano nunca vai a menos de + 8,7°.

Os valores diários mais frequentes de humidade são quase sempre superiores a 80 % e não raramente atingem a saturação. Por outro lado, o aparecimento do vento NW, quente e seco, faz com que a humidade atinja às vezes valores baixos 6-8 %, pelo que os valores médios sofrem um abaixamento considerável. Resumindo: um clima excessivamente húmido com alguns dias excessivamente secos.

O regime das chuvas é muito irregular, anos de grande pluviosidade, com totais excedendo 1 m, contrastam com anos em que ela é baixa, inferior a 40 cm. A média anual é de 757,2 cm, com 98 dias de chuvas (médias de 43 anos).

A transmissão da malária ocorre todo o ano, mas é mais intensa de Dezembro a Abril e baixa apenas durante 3 meses (Maio-Agosto).

B) POPULAÇÃO.

A população da cidade (área urbana e suburbana) é de 60 000 habitantes (censo de 1955), dos quais 28 699 são europeus, 569 indianos, 852 amarelos e 7334 mestiços; os restantes são de raça africana (22 546).

A população africana da área sub-rural está avaliada em, pelo menos, 70 000 e vivem também ali espalhados em pequenas concentrações cerca de 1667 não africanos (europeus, indianos e alguns da raça amarela).

C) TIPOS DE HABITAÇÕES.

Na área suburbana pulverizam-se 15 384 habitações, com um total de 28 704 compartimentos e 2964 capoeiras e estábulos rudimentares.

Encontram-se frequentemente nesta área casas rudimentares de paredes de madeira e zinco.

Na área sub-rural pulverizam-se um total de 9241 habitações, com 13 328 compartimentos, predominando as palhotas redondas cobertas a colmo, cujas paredes são cobertas de «mataca» e formadas por caniços. Pulverizam-se também nesta área 3539 capoeiras ou estábulos.

O total das habitações pulverizadas em cada campanha nestas duas áreas é de 24 625, com 42 032 compartimentos e 6503 capoeiras ou estábulos (média de 1706 compartimentos por casa).

D) BREVE RESUMO DAS CONDIÇÕES DA MALÁRIA SEGUNDO DADOS COLHIDOS HÁ 20 ANOS (1937).

A região de Lourenço Marques era ainda há 20 anos altamente hiperendémica, como ainda hoje acontece em numerosas regiões costeiras da África Oriental. Em 1937, num estudo por nós realizado em 6451 indivíduos de todas as raças, verificou-se um índice parasitário global de 35,48 %, assim distribuído:

QUADRO 1

Raças	Número de examinados	Número de parasitados	Percentagem
Europeus	1 696	75	5,71
Africanos	4 045	1 941	47,98
Mistos	710	252	35,49
Totais	6 451	2 290	35,48

O *P. falciparum* predominava em 98,02 % dos examinados, o *P. malariae* em 3,23 % e o *P. vivax* em 1,04 %; sòmente encontrámos 2 casos de *P. ovale*.

Os índices esplénicos andavam à roda de 60 % nas crianças e de 19 % entre os adultos.

Neste mesmo ano foi colhido em 15 estações de captura um total de 4616 fêmeas anofelíneas (3150 *A. funestus* e 1466 *A. gambiae)*, dando uma incidência de 10,5 por estação de captura.

Os índices esporozoíticos eram, respectivamente, de 7,9 (*A. funestus*) e 2,8 (*A. gambiae*).

A percentagem dos casos de malária no total das admissões no Hospital Central, entre os susceptíveis, ou seja entre os europeus, foi de 28,84 %.

E) DADOS MALARIOMÉTRICOS ANTES DO INÍCIO DA CAMPANHA IMAGOCIDA.

Estes exames incidiram em 4669 crianças de 30 escolas disseminadas pela cidade, nas zonas suburbana e semi-rural. Os índices esplénicos obtidos em 2072 crianças de 2-10 anos de todas as raças foi de 18,09 % com um baço hipertrofiado médio de 1,90. Os dados referentes aos adultos foram de 10,94 %, com um baço hipertrofiado médio de 1,54.

Se considerarmos sòmente as crianças africanas de 2-10 anos, o índice esplénico era de 23,78 %, o índice referente aos adultos era de 18,94 %.

Os índices parasitários nas diferentes raças, através também dos exames de escolas, eram de 50,16 % entre os africanos, 34,97 % entre os mistos, 6,19 % entre os indianos e 5,64 % entre os europeus.

Os índices parasitários entre os infantes (1-12 meses), que representam o melhor dado da transmissão que ocorre numa dada área, era de 39 % no período anterior ao início da campanha imagocida, em massa.

F) VECTORES.

O *A. funestus* e o *A. gambiae* são os únicos anofelíneos encontrados infectados na natureza e, portanto, os únicos que actuam como vectores.

Os seus lugares de criação são suficientemente conhecidos: o *A. gambiae* está mais ìntimamente relacionado com as chuvas e o *A. funestus* tem os lugares de criação mais permanentes nas pequenas correntes de água e nascentes.

Quanto à densidade dos vectores: o *A. gambiae* aumenta após o começo das chuvas, que é, em regra, no mês de Outubro, e atinge o seu máximo em Março. Durante a estação seca (Junho a Setembro) o *A. gambiae* diminui, atingindo o seu mínimo em Agosto. Nesta altura do ano o *A. funestus* predomina ($F/G = 9/1$), atingindo o seu máximo em Maio, mantendo assim a transmissão durante esta época do ano em que o número de *A. gambiae* está muito reduzido.

Nas estações de captura disseminadas pela área sob *contrôle* foram capturados (à mão) durante 5 anos antes da nossa campanha em massa, utilizando os insecticidas residuais, uma média anual de 3391 fêmeas

QUADRO 2 — *Densidade dos vectores — Fêmeas anofelíneas nas estações de captura*

Data	*A. funestus*	*A. gambiae*	Total	Média de *A. funestus* por estação de captura	Média de *A. gambiae* por estação de captura	Média de *A. funestus* + *A. gambiae* por estação de captura	Média de *A. funestus* capturados por dia/palhota	Média de *A. gambiae* capturados por dia/palhota	Média total de anofelíneos fêmeas capturados por dia/palhota
1945	4 189	1 495	5 684	523,625	186,875	710,500	1,434	0,511	1,946
1946	5 334	533	5 887	666,750	69,125	735,875	1,826	0,189	2,016
1947	3 096	349	3 445	387	43,625	430,625	1,060	0,119	1,179
1948	1 018	266	1 284	127,250	33,250	160,500	0,348	0,091	0,439
1949	154	504	658	19,250	63	82,250	0,052	0,172	0,225
Média por ano ...	2 758,2	633,4	3 391,6	344,7	79,1	423,9	0,951	0,216	1,161

anofelíneas, das quais 344 eram *A. funestus* e 79 *A. gambiae* (valores médios de 5 anos, com uma densidade total avaliada em 1,161 por dia/ /palhota — 0,951 *A. funestus* e 0,216 *A. gambiae* (quadro 2).

O índice esporozoítico variava entre 4,19 % - 2,60 % na estação das chuvas (estação da malária) e 1,17 % - 0,66 % na época seca (quadro 3).

QUADRO 3 — *Índices esporozoíticos na área de Lourenço Marques (médias de 5 anos) antes do* contrôle *(1945-1949)*

Meses	*A. funestus*	*A. gambiae*	*Funestus+Gambiae*
Janeiro	5,53	2,56	4,19
Fevereiro	3,98	3,35	3,15
Março	2,87	1,75	2,37
Abril	2,744	2,69	2,72
Maio	2,84	1,15	2,05
Junho	1,28	0,72	1,17
Julho	0,43	0	0,40
Agosto	0,84	0	0,80
Setembro	0,69	0	0,66
Outubro	1,57	0,66	1,38
Novembro	2,69	1,84	2,60
Dezembro	3,74	1,74	3,28

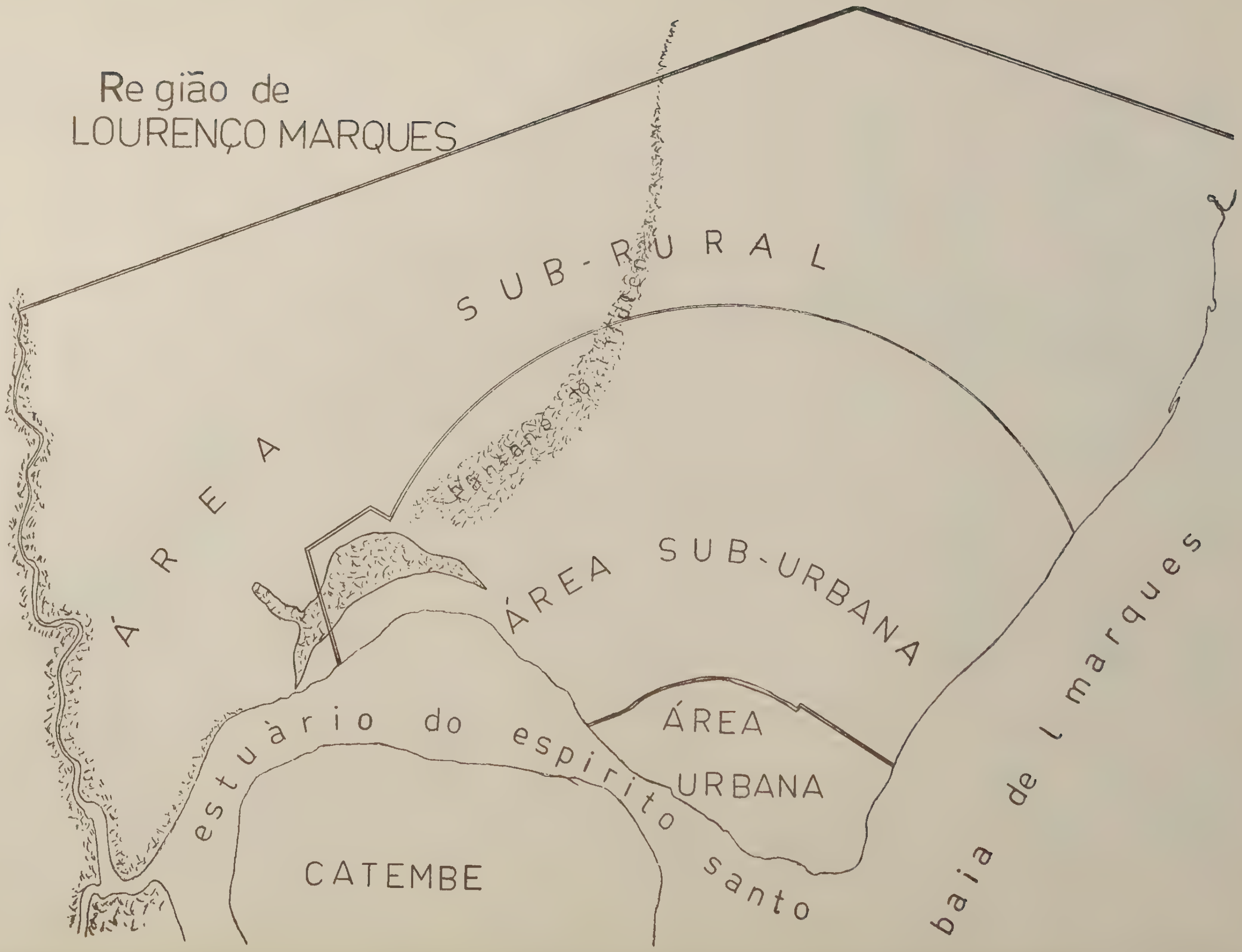
G) ORGANIZAÇÃO.

As medidas imagocidas constituem o nosso principal meio de combate na região suburbana e semi-rural. Tendo em vista o rápido aumento de lugares de criação de *A. gambiae* após o começo das chuvas, o tratamento das águas durante a estação seca não é econòmicamente de aconselhar.

Nas cidades como Lourenço Marques, onde a população está concentrada e onde as obras de saneamento e drenagem são econòmicamente possíveis e onde a vigilância pode ser eficaz, as medidas antilarvares são naturalmente realizadas.

A larga área sob *contrôle* (ver mapa) foi dividida em cinco zonas de pulverização, abrangendo a zona suburbana e a zona sub-rural num raio de 20 km fora dos limites da cidade.

Região de
LOURENÇO MARQUES


ÁREA SUB-RURAL
Pantano do Infulene
ÁREA SUB-URBANA
ÁREA URBANA
estuàrio do espirito santo
CATEMBE
baia de L marques

Esta campanha imagocida é feita por 3 brigadas, cada uma dirigida por um europeu devidamente treinado e composta por 10 trabalhadores indígenas treinados nas pulverizações.

Um destes indígenas é o encarregado de fazer as suspensões e encher as bombas.

Cada brigada de trabalho dispõe de uma camioneta de 1000 kg, que transporta o pessoal para os lugares de concentração, material e muitas vezes água, pois há locais (zona rural) onde o abastecimento é difícil.

Todos os dados referentes ao número de palhotas e compartimentos pulverizados e tipos de palhota são devidamente anotados por sinais convencionais mais acessíveis ao pessoal indígena.

As bombas que utilizámos são de tipo de mochila e de pressão dupla, accionadas por uma alavanca lateral, que é movida a ritmo de 20 bombadas por minuto.

A capacidade destas bombas é de 15 l, com uma mangueira de 1,5 m de comprimento, tendo na extremidade uma lança provida de um gatilho que contròla a saída do líquido, por um bico regulável que dá uma pulverização em leque.

Usámos principalmente como insecticida o hexacloreto de benzena (B. H. C.) sob a forma de pó molhável a 12 % de isómero gama. Na região suburbana, onde vive já uma população mais civilizada, que não aceita de bom grado o emprego de B. H. C., por lhes sujar o mobiliário, e sobretudo devido ao cheiro deste produto, utilizámos frequentemente um soluto a 5 % de D. D. T. em petróleo (2 g por metro quadrado de superfície).

São pulverizadas as paredes, tecto e face interna das abas das palhotas. Os galinheiros ou estábulos rudimentares que existem frequentemente nas aldeias indígenas são igualmente pulverizados.

A superfície média pulverizável de uma palhota rural é de 25,9 m^2. Utilizamos uma concentração que dá cerca de 400 mg de isómero por metro quadrado de superfície.

Fazemos assim duas campanhas anuais, uma iniciada em Outubro, e que se prolonga até fins de Dezembro, e outra iniciada em Janeiro, que se prolonga até fins de Março.

Cerca de 10 % das palhotas são encontradas fechadas, apesar de a população ser prèviamente avisada.

Isto não se deve a qualquer oposição às pulverizações, que os indígenas aceitam com o melhor agrado, pois os livra de outros insectos incomodativos. A razão principal é que esta população é muito móvel, grande parte dos homens trabalham na cidade, para onde têm de vir às primeiras horas da manhã, e bastantes mulheres têm de ir tratar das suas «machambas» e deixam as palhotas fechadas. Temos tentado reduzir ao mínimo este inconveniente, mas sem grande sucesso.

Naturalmente, a segunda campanha reduzirá este número, mas devemos confessar que mesmo assim fica sempre um certo número de palhotas sem tratamento.

As despesas com as campanhas, são as seguintes, tendo em conta os dados de 1956:

Insecticidas	194 611$19	= 44,2 %
Transporte	14 938$29	= 3,4 %
Pessoal	230 504$80	= 52,4 %
	440 051$28	

Custo *per capita* de toda a campanha antiadulto e antilarvar	3$81	(13 cent. U. S.)
Custo por palhota pulverizada com B. H. C.	3$25	(11 cent. U. S.)
Custo por compartimento pulverizado com B. H. C.	1$75	(6 cent. U. S.)

H) A COLHEITA DE DADOS MALARIOMÉTRICOS.

A colheita dos dados malariométricos consta de:

a) Procura semanal de anofelíneos num certo número de palhotas (estações de captura) pelo processo do lençol, utilizando um soluto de piretro. Devemos notar que este método não reflecte com segurança a ausência de vectores numa área, pois, apesar de uma aparente ausência de vectores dentro das palhotas, a transmissão ainda se faz, como se pode ver pelos índices parasitários dos infantes, se bem que devemos ter presente o carácter eminente migratório da população africana;

b) Colheita regular de amostras de sangue de infantes (1-12 meses);

c) Colheita de lâminas e medição dos baços em todos os grupos de idade, durante a época seca, para evitar o embaralhado de casos clínicos agudos, mais frequentes na estação das chuvas (quadro 10).

A malária não é ainda pela lei uma doença de declaração obrigatória, mas todos os casos com lâminas positivas que se registam nos serviços do Hospital Central são-nos notificados e são estudados epidemiològicamente, para procurar averiguar se eles são ou não presumidamente contraídos dentro da área sob *contrôle*. Os estudos biológicos que temos feito mostram-nos que não existe ainda qualquer sinal de resistência aos insecticidas ou mesmo um desvio evidente dos hábitos dos anofelíneos (exofilia).

I) RESULTADOS APÓS 6 ANOS DE COMBATE.

A campanha imagocida em massa nesta vasta área sob *contrôle,* que pormenorizámos atrás, utilizando principalmente o B. H. C. e, acessòriamente, em certas áreas da região suburbana, o D. D. T. a um ritmo de 3/3 meses em duas campanhas anuais, tem sido realizada desde 1950. Até essa data apenas tratávamos algumas zonas da região suburbana.

É interessante analisar os resultados após estes 6 anos de trabalho e em que medida eles se repercutiram nos vários sectores da população da cidade.

1 — Os efeitos sobre a morbilidade da malária podem ser avaliados pelos dados hospitalares e pelo número de casos registados e estudados epidemiològicamente. A leitura destes quadros mostra exuberantemente a grande melhoria de situação (quadros 4 e 5).

2 — Os dados malariométricos são mostrados nos quadros seguintes, tomando por base os exames feitos nas crianças em 37 escolas espalhadas pela cidade, subúrbios e zona semi-rural. Mostramos, para comparação, os dados obtidos antes e após 6 anos de *contrôle* (quadros 6, 7 e 8).

A rápida análise destes quadros mostra que a situação se modificou espectacularmente em 6 anos de combate. O índice parasitário, que antes do *contrôle* era entre as crianças escolares europeias de 5,64 %, baixou para 0; 6 anos após as pulverizações em massa da região, entre os africanos, que era de 28,01 %, baixou para 4,96. Na totalidade

QUADRO 4 — *Morbilidade e mortalidade da malária, segundo os dados do Hospital Central Miguel Bombarda, que recebe a maioria dos doentes da região de Lourenço Marques*

Anos	Admissões gerais	Casos de malária	Percentagem dos casos de malária nas admissões gerais	Mortalidade geral	Óbitos devidos à malária	Letalidade (%)
TODAS AS RAÇAS						
Antes do *contrôle*						
1942-1950	8 842 +	482 +	5,45 +	535 +	15 +	2,8 +
Depois do *contrôle*						
1951	11 462	246	2,1	682	9	3,6
1952	12 134	214	1,7	659	9	4,2
1953	12 586	261	2	663	11	4,2
1954	13 409	94	0,7	749	6	0,8
1955	15 773	205	1,2	788	11	1,3
1956	18 889	223	1,2	992	15	1,5
NÃO AFRICANOS						
Antes do *contrôle*						
1942-1950	3 084 +	367 +	11,9 +	535 +	7 +	1,3
Depois do *contrôle*						
1951	3 389	116	3,4	682	2	0,29
1952	3 709	137	3,6	659	3	0,45
1953	3 929	118	3	663	0	0
1954	3 815	49	1,2	749	1	0,13
1955	4 366	71	1,6	788	3	0,38
1956	4 517	70	1,5	992	1	0,1

+ Média anual.

(incluindo todas as raças) o índice parasitário, que era de 27,58 %, baixou para 2,37 %.

3 — *Efeitos sobre a transmissão* — Antes de estabelecer o *contrôle*, o índice parasitário dos infantes era de 31,6 % na região suburbana e 46,4 na região sub-rural. Nos últimos 4 anos (1954-1957) os índices parasitários entre os infantes andam à roda de 5-7 %, como se pode ver pelo quadro 9. Não se interrompeu a transmissão, mas têm-se reduzido consideràvelmente.

4 — *Dados entomológicos* — As investigações entomológicas, segundo a rotina atrás indicada, são mostradas nos seguintes quadros (n.ºs 11

QUADRO 5 — *Número de casos de malária registados no Hospital, confirmados por lâminas positivas e estudados epidemiològicamente*

Locais	Europeus	Africanos	Amarelos	Indianos	Mistos
1953					
Cidade	34	17	1	1	2
Zona suburbana	5	41	0	1	8
Zona semi-rural	5	7	0	0	5
Fora da área	73	63	0	3	17
Total	117	128	1	5	32
1954					
Cidade	7	4	0	0	1
Zona suburbana	0	7	0	0	3
Zona semi-rural	1	3	0	0	0
Fora da área	22	61	0	2	20
Total	30	75	0	2	24
1955					
Cidade	4	2	0	0	0
Zona suburbana	0	30	0	0	2
Zona semi-rural	2	28	0	0	2
Fora da área	49	194	0	1	37
Total	55	254	0	1	41
1956					
Cidade	5	1	0	1	0
Zona suburbana	2	6	1	0	0
Zona semi-rural	5	7	0	0	1
Fora da área	18	88	0	3	16
Total	30	102	1	4	17
1957					
Cidade	0	1	0	0	0
Zona suburbana	1	3	0	1	1
Zona semi-rural	0	0	0	0	1
Fora da área	4	22	0	0	8
Total	5	26	0	1	10

e 12), comparando os dados de antes e 6 anos depois da campanha imagocida em massa. Até 1952 as capturas eram feitas à mão; depois, dada a raridade dos vectores, passaram a ser feitas pelo processo do lençol, utilizando um insecticida de acção rápida.

Do exame destes quadros vê-se que a densidade dos vectores diminuiu progressivamente desde o começo da campanha imagocida em massa iniciada em 1950, mas sòmente ao fim de 4 anos de trabalho se conseguiu reduzir a um número negligível. Não conseguimos a erradicação de qualquer dos vectores.

QUADRO 6

Locais	Exam.	Parasit.	Percentagem	Esplenomegalia	Percentagem
Exames feitos nas escolas antes do contrôle					
Cidade	2 403	351	14,60	55	2,28
Zona suburbana	2 164	1 315	60,76	138	6,37
Zona rural	102	38	37,5	40	39,21
Soma	4 669	1 704	36,49	233	4,99
Exames feitos nas escolas 6 anos após o contrôle					
Cidade	4 909	5	0,10	—	0,46
Zona suburbana	6 442	250	3,88	9	0,86
Zona rural	469	26	5,54	11	2,34
Soma	11 820	281	2,37	283	2,39

Em 1956 ainda capturámos 14 fêmeas de *A. funestus* e 3 fêmeas de *A. gambiae* em 810 palhotas escolhidas ao acaso.

Os índices esporozoíticos têm sido sistemàticamente negativos desde 1953.

CONCLUSÕES

1 — Numa vasta região em parte semiurbana e em parte semi-rural, como zona de protecção para a cidade de Lourenço Marques, faz-se desde 1950 uma campanha imagocida em massa, utilizando o pó molhável de B. H. C. como insecticida residual, a uma dose de 400 mg por metro quadrado.

QUADRO 7 — *Resultados dos exames feitos nas escolas*

Idades	Europeus					Africanos					Mistos					Indianos					Amarelos					Totais				
	Exam.	Par.	I. P. (%)	Espl.	I. E. (%)	Exam.	Par.	I. P. (%)	Espl.	I. E. (%)	Exam.	Par.	I. P. (%)	Espl.	I. E. (%)	Exam.	Par.	I. P. (%)	Espl.	I. E. (%)	Exam.	Par.	I. P (%)	Espl.	I. E. (%)	Exam.	Par.	I. P. (%)	Espl.	I. E. (%)
Antes do contrôle																														
1- 5 anos	11	5	45,45	—	—	18	5	27,77	3	16,66	7	5	71,41	4	57,14	0	0	0	0	0	0	0	0	0	0	36	15	41,66	7	19,44
6-10 anos	929	55	5,92	15	1,61	951	534	56,15	294	30,91	353	111	31,44	64	18,13	189	10	5,29	2	1,05	35	0	0	1	2,85	2 440	710	29,09	376	15,40
11-15 anos	668	36	5,38	25	3,74	771	352	45,65	200	25,94	334	127	38,02	55	16,46	129	10	7,75	4	3,10	19	0	0	2	19,52	1 939	525	27,07	286	14,74
16-20 anos	104	0	0	1	0,96	95	29	29,47	18	18,94	13	4	30,76	1	7,69	20	0	0	2	10	7	0	0	0	0	238	33	13,44	22	9,24
+ 20 anos	7	1	14,28	0	0	3	2	100	0	0	5	2	40	0	0	1	0	0	0	0	0	0	0	0	0	16	5	37,5	—	—
Totais	1 719	97	5,64	41	2,38	1 838	922	50,16	515	28,01	712	249	34,97	124	17,41	339	21	6,19	8	2,35	61	0	0	3	4,91	4 669	1 228	27,58	691	14,79
Após 6 anos de contrôle																														
1- 5 anos	24	0	0	0	0	61	0	0	2	3,27	25	0	0	0	0	0	0	0	0	0	12	0	0	0	0	122	0	0	2	1,63
6-10 anos	1 852	0	0	0	0	1 329	93	6,99	66	4,96	707	5	0,70	4	0,56	933	3	0,32	4	0,42	60	0	0	0	0	4 881	101	2,06	74	1,51
11-15 anos	1 371	0	0	11	0,80	2 718	140	5,15	141	5,18	701	0	0	9	1,28	778	5	0,64	7	0,89	64	0	0	0	0	5 632	145	2,57	168	2,98
16-20 anos	333	0	0	6	1,80	576	35	6,07	24	4,16	112	0	0	6	5,35	79	0	0	2	2,53	49	0	0	1	2,04	1 149	35	3,94	39	3,39
+ 20 anos	16	0	0	0	0	10	0	0	0	0	1	0	0	0	0	5	0	0	0	0	4	0	0	0	0	36	0	0	0	0
Totais	3 598	0	0	17	0,47	4 694	268	5,70	233	4,96	1 546	5	0,32	19	1,22	1 795	8	0,44	13	0,72	189	0	0	1	0,52	11 820	281	2,37	283	2,39

QUADRO 8

Idades	Exam.	Par.	Percentagem	Falc.	Percentagem	Viv.	Percentagem	Mal.	Percentagem
AFRICANOS E MISTOS									
Antes do contrôle									
1-10 anos	1 329	657	49,2	646	98,23	16	2,08	8	1,04
10-15 anos	1 105	479	43,35	478	99,79	8	2,19	2	0,54
+ 15 anos	116	37	31,89	37	100	0	0	0	0
Soma	2 550	1 173	46	1 161	98,97	24	2,94	10	0,85
Após 6 anos de contrôle									
1-10 anos	4,591	129	2,80	121	93,79	3	2,32	4	3,10
10-15 anos	1 402	120	8,70	116	95,08	1	0,83	3	2,50
+ 15 anos	378	24	5,82	22	91,66	0	0	2	8,33
Soma	6 371	273	4,28	259	94,87	4	1,46	9	3,29
EUROPEUS									
Antes do contrôle									
1-10 anos	940	60	6,38	60	100	0	0	0	0
10-15 anos	668	36	5,38	35	97,92	1	0,15	0	0
+ 15 anos	111	1	0,90	1	100	0	0	0	0
Soma	1 719	97	5,68	96	98,96	1	1,03	0	0
Após 6 anos de contrôle									
1-10 anos	2 348	0	0	0	0	0	0	0	0
10-15 anos	1 014	0	0	0	0	0	0	0	0
+ 15 anos	23	0	0	0	0	0	0	0	0
Soma	3 598	0	0	0	0	0	0	0	0

QUADRO 9 — *Índices parasitários dos infantes (1-12 meses) na região de Lourenço Marques*

Anos	Número de examinados	Região suburbana (I. P.)	Região rural (I. P.)	Total da área (I. P.)
Média de 5 anos antes do *contrôle*	635	31,6	46,4	39
1952	186	7,6	6,9	7,4
1953	351	10,4	22,5	14,5
1954	867	3,6	8,3	5,98
1955	848	2,81	7,21	5,31
1956	1 311	6,79	7,67	6,73
1957	622	7,22	7,27	7,24

QUADRO 10 — *Exames feitos nas zonas suburbana e sub-rural numa amostra média de 3175 exames anuais, ou seja, em 3,43 % da população da área*

Idades	I. P.	I. G.	I. R.
		1953	
0- 1 ano	7,59	1,9	5,9
2- 5 anos	16,21	3,6	13,36
6-10 anos	15,16	2,8	12,1
11-20 anos	11,27	1,9	7,8
21-30 anos	0	0	0
+ 30 anos	0	0	0
Média	8,37	1,70	6,52
		1954	
0- 1 ano	11,3	22	1,2
2- 5 anos	17,5	29,8	5,4
6-10 anos	16,4	22,3	6,5
11-20 anos	6,8	18,1	3,4
21-30 anos	3,7	0	0
+ 30 anos	2,2	20	0
Média	9,65	18,70	2,75
		1955	
0- 1 ano	6,96	1,96	0
2- 5 anos	17,19	5,28	6,18
6-10 anos	12,26	3,55	3,84
11-20 anos	7,62	0,92	0,92
21-30 anos	3,35	0,25	0
+ 30 anos	3,57	0,54	0,27
Média	8,49	2,08	1,86
		1956	
0- 1 ano	7,15	2,78	0,19
2- 5 anos	12,25	4,52	0,89
6-10 anos	12,15	1,97	3,34
11-20 anos	1,33	0,75	1,25
21-30 anos	2,89	0,26	1,05
+ 30 anos	1,58	0,22	0
Média	6,22	1,75	1,12
		1957	
0- 1 ano	2,59	1,03	0,51
2- 5 anos	11,47	3,89	2,25
6-10 anos	12,95	4,44	0,38
11-20 anos	4,85	1,45	0,48
21-30 anos	4,59	1,02	5,10
+ 30 anos	4,85	29,12	0
Média	6,88	6,82	1,45

I. P. — Índice parasitário.
I. G. — Índice gamético.
I. E. — Índice esplénico.

QUADRO 11 — *Média anual da densidade dos vectores: capturas por palhota antes e durante 6 anos de* contrôle

Espécies	1949	1950	1951	1952	1953	1954	1955	1956
A. funestus	5,17	3,9	4,4	1,7	0,02	0	0,045	0,017
A. gambiae	2,27	1,5	0,5	0,1	0,3	0	0,081	0,0037
Funestus + *gambiae*	7,44	5,4	9,9	1,8	0,32	0	0,12	0,012

QUADRO 12 — *Índices esporozoíticos da região de Lourenço Marques*

Anos	*A. funestus*	*A. gambiae*	*Funestus* + *gambiae*
1940-1945 (média anual)	7,9	2,8	10,7
1949	4,7	3	7,7
1950	0,7	1,8	2,5
1951	0,4	1	1
1952	0,4	0	0,4
1953	0,2	0	0
1954	0	0	0
1955	0	0	0
1956	0	0	0

2 — Após 6 anos de pulverizações, conseguimos reduzir a malária a um grau que já não representa um problema para a população.

3 — A morbilidade da malária na população local, avaliada pelos dados hospitalares, baixou de 5,45 % nas admissões gerais para 1,2 %.

Entre os europeus essa percentagem baixou de 11,9 % para 1,5 %.

4 — O número de casos de malária registados dentro da área sob vigilância confirmados laboratorialmente entre os não imunes (europeus) foram, em 1953, em número de 44. Em 1957 apenas se registou um caso.

5 — Um exame feito nas crianças escolares antes do *contrôle* mostrou que, no total, 36,49 % se encontravam parasitadas. Em 1957 o índice parasitário foi reduzido para 2,37 %. Entre as crianças europeias antes do *contrôle*, o índice parasitário foi de 5,68 %; em 1957 nenhuma criança europeia das escolas foi encontrada infectada

6 — Apesar de 6 anos contínuos de aplicação de insecticidas residuais, não conseguimos a erradicação de qualquer dos vectores, embora a densidade tenha sido reduzida a um número muito baixo.

7 — Não conseguimos interromper a transmissão, embora tenhamos reduzido os índices parasitários, entre os infantes, de 31,65 % para 6-7 %.

8 — A corrente migratória da população africana deve ser a responsável por muitos dos casos de malária observados dentro da área, e isto é um factor importante a ter presente quando se avaliam os resultados obtidos.

9 — Não nos parece possível, dentro das condições climáticas das zonas costeiras da África Oriental e dados os hábitos migratórios da população, interromper a transmissão numa área restrita, utilizando apenas um insecticida residual em duas campanhas anuais com 3 meses de intervalo.

A transmissão ocorre principalmente durante os meses de Dezembro a Abril.

Durante os meses de Maio a Setembro a transmissão é muito baixa.

PROBLEMS OF PHYSICS AND CHEMISTRY OF RESIDUAL INSECTICIDES

R. A. E. Galley

In spite of the excellent work carried out on swamp drainage, screening of buildings and the use of pyrethrum sprays, an economic attack against the vectors of malaria in rural areas was not practicable until the discovery of the «residual» contact insecticides. These insecticides, of which DDT was the first to be discovered and put to practical use, are, as their name implies, biologically active chemical compounds of low vapour pressure which are inert to light, atmospheric oxygen and water vapour.

The chemicals themselves and the formulations made from them can be submitted to chemical and physical tests which enable their suitability for use in malaria control programmes to be determined. The World Health Organization started its work on specifications and methods of analysis for insecticides in 1949 (1). The latest World Health Organization document on specifications was published in 1956 (2). Many of the methods of examination are fairly simple, basic and straightforward, e. g. chlorine determinations, melting point and ash content while others are of a more empirical nature often not so simple and require prolonged experimentation before the test procedure and limits can be finally defined. I will give you just one example. In most mosquito control projects water-dispersible powder formulations are used. These need to have certain properties for them to be of any use in the field. Two of these are extremely important. One is the dispersion stability, and the other is the ability to withstand tropical storage without losing either (*a*) its content of active ingredient by decomposition or (*b*) its dispersion stability when prepared for use. It is quite obvious that it is impossible to submit each batch of insecticide bought for a malaria control project to an actual tropical storage test. We have, therefore, to devise laboratory tests which accelerate the tropical storage artificially and to correlate the results of actual tropical storage with those empirical accelerated tests.

In recent years the World Health Organization has sponsored storage trials in Nigeria and arranged for analysis on samples drawn at regular intervals to be carried out in different laboratories in Europe and America. In this way, both the repeatability of the tests in different laboratories is being determined and valuable data collected on the behaviour of different insecticides formulations under known conditions of tropical storage. The data are now being processed for consideration at the next meeting in November of the World Health Organization Expert Committee on Insecticides.

The setting of limits is, up to a point, arbitrary but one aims always at compromising between cost and performance requirement. It is obviously pointless to insist on having a formulation which would remain stable in suspension for two hours if the cost of producing it is much higher than one which is stable for say twenty minutes, the average time taken for emptying a knapsack sprayer. It is equally pointless to accept, because it is cheap, a formulation which settles to the bottom of the sprayer as soon as it is prepared for use.

The first chemical and physical problems are therefore those concerned with ensuring that the supplies purchased for a control campaign will in fact do what is wanted of them.

Next, for the control campaign to be successful, the insecticide must be brought into effective contact with the insect vector of the disease. Factors which may affect the duration and efficiency of the deposits are:

1. The nature of the surface.
2. The form in which the insecticide is applied.
3. The particle size of the insecticide.
4. The uniformity of the deposit which is dependent upon:
    - *a*) the physical characteristics of the insecticide suspension or emulsion,
    - *b*) the spraying apparatus with which it is applied and
    - *c*) the application technique.

The specification for the insecticide, if drawn up correctly, will minimise the variations likely to arise under 2, 3 and 4 (*a*), while the specification for the spraying apparatus can help to look after excessive variation under 4 (*b*). Mr. Knipe will be dealing with spraying apparatus later so I will not anticipate what he will be saying. With adequate training and supervision of the spray operatives, variation under 4 (*c*) can be reduced to a minimum.

This leaves 1, the nature of the surface, which cannot be specified. Dwelling huts in rural areas are made from indigenous materials and, over wide areas in the tropics, this means mud and thatch. For obvious reasons of transport this means mud made from local soils some of which are highly active in their powers of sorbing insecticides. The red soils, of high iron contest, are particularly active in this respect, and insecticides applied to them, even in the form of water dispersible powders, rapidly disappear from the surface, being sorbed into the subsurface layers of the mud. The photograph shows this very clearly. The loss of insecticidal activity of DDT on such surfaces was originally attributed to catalytic decomposition of the DDT by the iron in the mud.

My colleagues Barlow and Hadaway (3, 4, 5), however, showed that the insecticide could be recovered quantitatively from mud and that the phenomenon was purely physical. Further, the complete extraction of the iron from the mud only impaired its sorbtive capacity slightly.

Sorption appears to take place in two stages, during the first of which the insecticide is concentrated in the layers immediately below the surface. This stage takes place fairly rapidly and is followed by a slower diffusion stage which finally results in the insecticide becoming evenly distributed throughout the mud block. The diffusion rates of different insecticides are in the same order as the initial sorption rates. γ-BHC became evenly distributed through an experimental mud block in 8 weeks. Dieldrin took 12 months to reach the same evenness of distribution through an identical block. Dieldrin was sorbed slightly more rapidly than DDT but appeared to diffuse at about the same rate.

Once sorbed, the insecticide is held much more firmly than it is, for example, if it is sprayed on a glass plate. There was no appreciable loss of dieldrin during the twelve month period in which it diffused through the mud block whereas 90 % of a deposit of the same magnitude was lost from a glass surface in that period. Loss of the much more volatile γ-BHC was also considerably slower from a mud than from a glass surface. In fact, the longer life of BHC under field conditions than would have been expected from its physical properties can be accounted for by its sorption by mud and slow desorption.

While these studies were in progress field observations by Bordas and Navarro (6) in Central America and Burnett (7) in East Africa showed that sprayed surfaces which had partly lost their efficacy showed an increase in biological activity with an increase in humidity. My colleagues turned their attention in the laboratory to studies of the effects of humidity on sorption and the biological efficacy of sprayed surfaces and they confirmed the field results and in addition revealed interesting differences in the effects of humidity on the two stages of sorption and also slight differences in the behaviour of DDT on one hand and dieldrin on the other.

The rate of disappearance of the insecticide from the mud surface (first stage) was inversely related to humidity while the rate of diffusion (stage 2) was directly related to humidity. Thus after the initial sorption, an increase in humidity increases the mobility of the insecticide which results in more rapid diffusion inward from just below the surface and also presumably a greater potential for diffusion in insects resting on the mud surface.

It is in the second diffusion stage that differences were detected between DDT and dieldrin. If after application and first stage sorption at low humidity, the humidity is raised there is an apparent movement of some DDT back towards the outermost layers of mud as well as inwards. The «abnormal» fraction persisted in the outer layer for the eight weeks of the experiment. This phenomenon was not observed with dieldrin or γ-BHC and will be studied further.

Although theoretical speculation of the effects of sorption on mosquito control is possible it is not known to what extent sorption has had a detrimental effect on a malaria control project.

It can be argued, as far as BHC is concerned, that a beneficial effect results as the insecticide is not lost so quickly as it otherwise would be.

However, in view of the theoretical possibility of the loss of efficiency of the less volatile insecticides as a result of sorption, some manufacturers have devoted their attention to the development of longer lasting formulations. On the one hand dieldrin formulations need to resist sorption while on the other BHC formulations need to hold the BHC longer on non-sorptive surfaces.

After encouraging results in the laboratory with dieldrin formulations field trials were arranged at our laboratories in Arusha, Tanganyika Territory, but the encouraging laboratory results were not repeated in the field. It is obvious that much more work needs to be done before this anomaly is explained.

Field trials with BHC formulations have been started at Arusha after encouraging laboratory results, but they have not gone far enough for conclusions to be drawn.

The main problem of what effect sorption has on a malaria control programme has yet to be determined. Experiments to obtain preliminary data on this subject were considered at the W. H. O. headquarters at Geneva in July 1957 when it was agreed that bio-assays and chemical analyses of the walls of test huts would be made at intervals after the initial spraying. The huts would be chosen to represent those made from highly, medium and poorly sorbant soils and to simplify the experiment the interior surface would be specially smoothed to facilitate the bio and chemical analytical procedure.

Here again we have problems of how to determine chemically the amount of insecticide that is *available to the insect*. Several workers have investigated this problem including my colleague Barlow (8) at Porton and Professor Alessandrini (9) of the Istituto Superiore de Sanità, Rome, who I believe is here today and will I hope speak about her work during the discussion.

Now I would like to say a few words about mechanisms of toxicity — a subject on which Dr. Hadaway would have spoken, had he been able to attend.

It would be correct to say, I think, that the development of insecticide resistant strains of insects among pests of public health importance has stimulated more work on the mode of action of insecticides than would otherwise have been undertaken.

Many of the observations therefore refer to comparisons between «resistant» and «normal» strains of insects and, as the resistance developed by houseflies has been so spectacular the world over, studies on these insects figure largely in the literature.

Dr. Busvine will be dealing with the general question of resistance. The physical and chemical aspects we have to consider are the «pick-up» of the insecticide by the insect, the penetration of the insecticide through the cuticle, its distribution within the insect and its fate chemically after distribution. It will be apparent from the above that abnormalities in a group of insects in any one of these processes concerned with the metabolism of insecticides could confer a difference between the susceptibility of the insects in that group and the species as a whole. Thus, dealing with DDT and houseflies, the resistant strains at Basle have been shown by Reiff and Wiesmann (10) to contain more total lipoid than «normal» populations. This enables more DDT to be dissolved and thus protects the more sensitive tissues where its effect might otherwise be lethal.

Kearns and his collaborators (11) have shown that the main factor conferring DDT resistance in houseflies is the presence of the enzyme DDT-dehydrochlorinase which enables the fly to convert DDT to the harmless ethylenic derivative DDE. They showed that the inheritance of DDT resistance in the F_2 and back crosses between their resistant and susceptible strains was exactly in line with the inheritance of DDT--dehydrochlorinase.

Bradbury (12) has shown that BHC resistant houseflies have been shown first to pick up less BHC than the normal strain and secondly to convert it more quickly to excretable water-soluble metabolites. Eleven water soluble metabolites have been detected (but not identified) by Bradbury. In this connexion Kearns has stated that the first metabolite is the dehydrochlorinated compound pentachlorocyclohexene, although the enzyme which brings about this dehydrochlorination is not DDT dehydrochlorinase.

Turning to mosquitoes, the DDT resistant *A. sundaicus* from Eastern Java owe their resistance to the presence of DDT dehydrochlorinase which is absent from the mosquitoes of normal susceptibility. On the other hand, DDT resistant *Aedes aegypti* from Trinidad possess the power of converting DDT to DDE although Brown (13) was unable to demonstrate the presence of DDT dehidrochlorinase *in vitro* by methods by which its presence in resistant houseflies had been demonstrated.

Further knowledge of the mechanisms by means of which insects are able to avoid the more usual effects of insecticides could well provide us with means of overcoming some forms of insect resistance.

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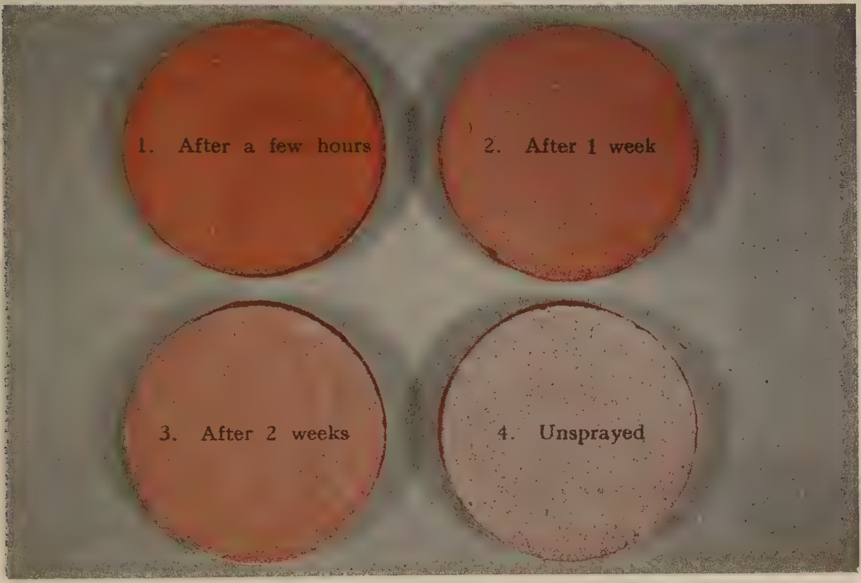
Uganda mud blocks, sprayed with a 75 % DDT wettabile powder st 200 mg/sq. ft.


1. After a few hours
2. After 1 week
3. After 2 weeks
4. Unsprayed

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GENERAL DISCUSSION

Dr. L. J. Bruce-Chwatt U. K.) — The speaker congratulated Dr. Mastbaum on his paper and mentioned the problem of age determination of adult mosquitoes. He traced the history of the technique developed of by the Russian workers Detinova and Polovodova. It is used on a large scale in U. R. S. S. for epidemiological assessments of malaria control programmes. Only recently have the Western malariologists understood the value of this method and work by Gillies, Bertram and others has proved its value.

Dr. A. Gabaldon (Venezuela) — In reference to exophily in anophelines I want to emphasize the importance of out-of-doors transmission which may be result from indoor-biters and outdoor-resters, or outdoor-biters and outdoor-resters. In several parts of South America the present difficulty in obtaining total interruption of transmission is due to such characteristics being present in the responsible vectors. As those anophelines are also indoor-biters and indoor-resters transmission is considerably reduced with the insecticides, but does not come to an end. The study of these facts is of great interest since the very beginning of the spraying program, because if transmission continue in spite of the insecticide, additional measures should be introduced early or the program may be unnecessarily delayed. This problem will probably be found in other areas.

Dr. Ernest Paulini (Brazil) — I want to congratulate Dr. Galley on his fine presentation of the problem caused by the sorption of insecticides on mud surfaces. We have been working on this problem in Brazil and were wondering how great this problem would be in the field, therefore we have started to collect mud samples from various areas of Brazil and tested them for sorptive capacity. In the past three years we have tested over 300 mud samples and the results in rough figures are the following: 25 % of the samples have shown high sorptive capacity, 50 % medium and 25 % low sorptive power. I think similar investigation in other conutries will supply valuable information for the men responsible for malaria eradication program.

Dr. FERNANDO M. DE BUSTAMANTE (Brazil) — I just want to confirm the information given by Dr. Gabaldon on the existence of certain problems in South American where house spraying with insecticides may not interrupt transmission completely.

In Brazil we have such problems in areas with transmission by *A. cruzii cruzii* and by *A. darlingi*.

Dr. GEORGE GIGLIOLI (U. K.) — In the course of his communication Prof. Van Thiel referred to race as a factor influencing the epidemiological classification of malaria on the basis of splenic enlargement; he also mentioned the sickling trait as possibly related to the peculiar reaction of the negro race to intensely endemic malaria.

In British Guiana several races live side by side under identical conditions of exposure to infection: East Indians, Negroes and smaller numbers of Amerindians, Portuguese and Chinese. The splenic reaction of Negroes, at all ages, was always very much less conspicuous than in the other races, particularly the East Indians and Amerindians. This applied not only to the Guianese Negroes but to recent immigrants from Barbados as well, where only a short malarial episode was registered in 1925.

East Indians, on the contrary, however heavily exposed to infection continued to carry large spleens throughout life. The same applied to Amerindians. In Surinam Swellengrebel reported holoendemic malaria among Bush Negroes on the Waiombo River, who live in conditions entirely similar to those of our riverine populations of Mixed or Amerindian race.

In British Guiana no survey has been made for the sickling trait; in 36 years experience however one single observation of sickle-cell anaemia has come to my notice and that in a Portuguese family.

Dr. E. PAMPANA (Italy) — Notes that the cost of U. S. $ 0.11 per hut protected by residual spraying is very low for Africa, if it entails two sprayings a year.

As regards Dr. Galley's paper and some of the hypotheses he brought forward he would add that of needing a B. H. C. preparation with a longer residual power, which would prolong the activity on non sorptive material (such as the thatched roofs), without interfering with the usual fumigating action of B. H. C., which is rather long lasting on sorptive material (such as the mud walls). This preparation might well be extremely useful for most rural houses of Africa.

Dr. E. PAMPANA (Italy) — Expresses the wish that, if their suggestion is followed, (i. e., giving up spleen rate as a yardstick) a new set of terms should be proposed by them rather than applying the terms of «hypoendemic», «mesoendemic», «hyperendemic» and «holoendemic» malaria. These terms are mainly based on spleen rates and it would create confusion to use them on the basis of parasite rate findings.

Dr. MARIA ESTER ALESSANDRINI (Italy) — As mentioned by Dr. Galley, I carried out some tests regarding the residual action of DDT on mud walls. The samples, seven in number, coming from some countries of the Middle East and were sent by W. H. O. The purpose was to observe the residual action of DDT. Chemical tests were carried out by myself and my co-workers and biological tests by Dr. Mosna.

The results obtained by chemical and biological tests were completely in agreement. Furthermore, they correspondent with the results obtained by Dr. Galley, that the lost of biological activity was not attributed, as before supposed, to the dechlorination of DDT, but to the absorption of the insecticides, depending on the kind of material. But I was unable to ascertain the factor responsable for the absorption, i. e. the correlation between absorption and physical or/and chemical properties of the different materials.

The results obtained by Dr. Galley in relation to humidity are the most interesting.

Another point to take into consideration regarding residual of insecticides in the walls, is how to carry out the sampling. By the method of scraping, even though a very thin layer is taken, as must be done, more may be scraped off that is utilized by the insects. Consequently a very good method is required which removes only superficial insecticide. Until now we have three such methods; the Hadway and Barlow method consisting in a strip of cellotape; my own consisting of parchement paper coated with a kind of silicone; and the Shell method consisting of methylcellulose. All of these three methods have some advantages as well as some desadvantages. So we need and we are looking for a better method. Now, one of my co-workers has prepared a new material and I have given samples to Dr. Pampana, Dr. Bruce-Chwatt, Dr. Treboux, Shell Co. and others to try this new method in order to establish whether it is better than those now in use.

2ND SESSION — *Thursday* — *September, 11th,* — *11:00 to 12:30 a. m. Room D*

The meeting was held under the Chairmanship of Dr. E. J. Pampana and Dr. Botha de Meillon.

The Rapporteur was Dr. O. Mastbaum and the Secretary was Dr. Jorge Melo Vieira.

The following papers were presented and discussed:

DONNEES RECENTES SUR LA DISTRIBUTION ET LES CARACTERISTIQUES ECOLOGIQUES DES VECTEURS DU PALUDISME DANS LE MONDE

J. HAMON

Au cours des dernières années il n'y a pas eu de modifications marquées dans nos connaissances concernant la distribution des anophèles vecteurs du paludisme. La majorité des informations nouvelles proviennent des révisions systématiques des groupes *umbrosus* Theo. et *hyrcanus* Pall. par Reid, et du groupe *leucosphyrus* Dönitz par Colless, et n'ont pas de répercussions importantes au point de vue de l'étude de la transmission. Par contre, la fréquence relative des espèces a été modifiée en de nombreuses régions par l'emploi massif des insecticides. Nous étudierons ce phénomène conjointement avec les caractéristiques écologiques des vecteurs intéressés.

Au fur et à mesure que s'étendent les campagnes visant à l'éradication du paludisme on constate que le comportement des vecteurs est beaucoup plus varié qu'on ne le soupçonnait auparavant, et que l'étude de ce comportement est indispensable pour conduire les campagnes en cours avec un maximum d'efficacité. Dans beaucoup de cas, en effet, les recherches faites avant le house-spraying se sont avérées insuffisantes pour expliquer l'inefficacité relative des insecticides. Nous nous trouvons donc devant une masse considérable de documents qu'il est impossible de résumer ici, et nous nous contenterons de présenter quelques unes

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des observations illustrant la complexité du comportement des vecteurs du paludisme en différents points du monde, en insistant plus particulièrement sur ceux dont le contrôle n'a pu encore être réalisé de façon satisfaisante à l'aide des insecticides à action rémanente.

Dans les zones à broméliacées epiphytes d'Amérique centrale et du sud, principalement au Brésil et à Trinidad, les anophèles du sous-genre *Kerteszia,* en particulier *A. cruzii* D. et K. et *A. bellator* D. et K., attaquent l'homme pendant la journée et au crépuscule, principalement à l'extérieur des habitations. Ils sont très anthropophiles, et, avant l'emploi des insecticides, étaient nettement endophiles (Rachou). Depuis le house-spraying les femelles sont devenues 10 fois plus rares sur les parois intérieures traitées des habitations, mais 5 fois plus fréquentes sur les parois extérieures non traitées, et la transmission du paludisme continue (Ferreira et coll.). L'arrêt de la transmission nécessite la destruction des broméliacées epiphytes à l'aide de pulvérisations cupriques dans un large rayon autour des plantations et des habitations, la portée de vol efficace d'*A. cruzii* étant bien supérieure à un kilomètre (Rachou, Ferreira).

En Amérique Centrale *A. aquasalis* Curry est un vecteur assez important de la latitude 23° Sud jusqu'à l'équateur, et dans quelques îles au nord du 10ème degré de latitude Nord, alors qu'il est mauvais vecteur entre l'équateur et le 10ème degré da latitude Nord. Il s'infecte cependant facilement au laboratoire avec *Plasmodium falciparum* et *P. vivax* et, en Guyane Française tout au moins, sa mortalité quotidienne moyenne ne semble pas dépasser 10 % (Floch). Comme il est très *exophile* et attaque principalement au crépuscule, alors que les hommes ne sont pas encore enfermés dans leurs habitations, on aurait pu s'attendre à ce qu'il soit difficilement contrôlable par les aspersions d'insecticides. Il n'en est rien car sa zoophilie est intense, 2 à 6 % seulement des femelles se nourrissant sur l'homme (Gillette), et la transmission du paludisme n'est assurée que lorsque l'espèce est excessivement abondante (Senior White). Il s'ensuit que toute mesure faisant diminuer la densité anophélienne de façon marquée, soit la lutte antilarvaire, soit le house-spraying, suffit à arrêter la transmission (Gillette).

Dans le nord de l'Amérique du Sud *A. darlingi* Root est un des meilleurs vecteurs du paludisme. Son endophilie et son anthropophilie vont en croissant du Brésil central, où 30 % environ des repas sont pris sur l'homme, vers les régions périphériques de son aire de répartition, Guyanes, Bolivie et Centre Nord Vénézuéla, où son anthropophilie est à peu près totale. Partout le house-spraying a arrêté la transmission du paludisme, mais dans le Brésil central *A. darlingi* continue à pulluler à l'extérieur dans les zones traitées, alors qu'il semble avoir été éradiqué dans les régions périphériques. En fait diverses observations montrent que, même dans ces régions, *A. darlingi* continue à exister en forêt à l'état sauvage. Cette exophilie n'est probablement pas une conséquence de l'emploi des insecticides, car, en Guyane Française tout au moins, *A. darlingi* constituait, avant les aspersions, 12 % des anophèles adultes rencontrés en forêt, parfois à plusieurs journées de marche des habitations les plus proches (Floch). C'est une espèce susceptible d'expansion rapide, qui en un temps court peut, à partir de gites résiduels, repeupler des centaines de kilomètres en suivant le cours des rivières (Rachou et coll.). Tant qu'il restera des porteurs de gamètes dans la population il faudra donc maintenir une surveillance constante, même dans les zones où il semble avoir disparu, afin d'éviter sa réinstallation et la reprise de la transmission. L'invasion récente d'une zone littorale de la Guyane Britannique, d'où il avait été éradiqué, laisse penser qu'il ne s'agit pas de deux races biologiquement différenciées, puisque les *A. darlingi* exophiles et zoophiles d'origine forestière arrivant dans une zone habitée par l'homme ont immédiatement manifesté leur endophilie et leur anthropophilie (Giglioli et Charles).

A. albimanus Wied. a été l'objet d'observations intéressantes. C'est un moustique exophile, mais relativement endophile et anthropophile. A Panama, où il était un vecteur important, chaque campagne de house--spraying entrainait habituellement une forte diminution de la densité de cette espèce, et une mortalité élevée des femelles gorgées posées dans les maisons. Or dans des villages traités respectivement déjà 15 et 20 fois au DDT, Trapido a constaté que les aspersions n'étaient plus suivies par une mortalité importante des femelles gorgées, ni par une diminution de la densité d'*A. albimanus*, bien que la susceptibilité au DDT de cette espèce soit la même dans ces villages traités que dans les villages jamais traités. Le pourcentage des femelles gorgées restant très faible, on peut supposer qu'*A. albimanus* est devenu hyperirritable ou DDT et quitte les surfaces traitées bien avant d'avoir été mortellement intoxiqué, ce qui pratiquement l'amène à ne plus se gorger sur l'homme à l'intérieur des habitations, et entraine une déviation zoophile. Au Vénézuéla Gabaldon a d'ailleurs constaté que la réduction de densité de cette espèce à la suite de campagnes de house spraying était d'autant plus accentuée qu'il y avait plus d'animaux et moins d'habitants, et n'aboutissait pas à l'éradication du vecteur, bien que la transmission du paludisme soit interrompue.

Les observations de Trapido (1954) concernant la résistance de comportement chez *A. albimanus* de Panama ont été tout dernièrement confirmées par Brown qui a démontré que le temps d'excitation expérimental des femelles de cette espèce est moindre dans les régions précédemment traitées au DDT que dans les autres où cet insecticide n'a pas été employé.

Dans le Bassin méditerranéen *A. labranchiae* Falleroni était un des grands vecteurs du paludisme, et passait pour très endophile et très anthropophile. Le house-spraying, parfois accompagné de lutte antilarvaire, a arrêté la transmission et entrainé presque partout une quasi-éradication de l'espèce. Mais des enquêtes entreprises après les campagnes d'aspersion ont montré l'existence en Sicile (D'Alessandro, Mariani) et en Sardaigne (Cefalu) d'adultes entièrement exophiles, vivant dans les crevasses de rocher, sous les berges des rivières, parfois à une altitude élevée, et à une grande distance des habitations humaines. En Sardaigne la raréfaction d'*A. labranchiae* a été suivie par l'expansion d'*A. hispaniola* Theo. (Trapido et Aitken), probablement parce que les adultes de cette dernière espèce étaient plus exophiles et parce que leurs larves vivaient dans des cours d'eau assez rapides où l'emploi des larvicides est malaisé et peu efficace. En outre la vitesse avec laquelle *A. hispaniola* envahit les zones d'où les anophèles avaient été éliminés est beaucoup plus élevée que celle des autres espèces vivant en Sardaigne, et peut être en moyenne de 3,4 kilomètres par semaine (Loddi et coll.). La plupart de ses anciens gîtes étant actuellement occupés par *A. hispaniola, A. labranchiae* reste localisé et peu abondant malgré l'interruption des traitements insecticides.

En Jordanie et en Israel l'élimination par le house-spraying des vecteurs principaux, *A. superpictus* Grassi et *A. sacharovi* Favr. a mis en évidence dans certaines régions le role vecteur d'*A. sergenti* Theo. Cet anophèle pique la nuit à l'intérieur comme à l'extérieur des habitations et des tentes et s'abrite ensuite dans les fissures du sol et dans les grottes qui semblent ses lieux de repos préférés, même lorsqu'il y a des habitations non traitées dans les environs. Dans les endroits où ces abris naturels sont rares, comme la partie Sud de la vallée du

Jourdain, le traitement des habitations et des tentes arrête la transmission du paludisme (Farid), mais dans les zones de collines calcaires où les anfractuosités du sol sont nombreuses la transmission continue malgré les aspersions (Farid, Saliternik), et la lutte antilarvaire semble être la seule méthode efficace contre *A. sergenti*. Cette lutte antilarvaire est cependant très délicate à conduire si l'on veut éviter de créer des souches résistantes chez les autres anophèles vecteurs actuellement sous contrôle, notamment *A. sacharovi*.

En Israel *A. claviger* Meig. pose un problème identique dans une zone très limitée. Cette espèce qui n'est pas vectrice dans la partie Ouest de son aire de répartition, et jouait un role mineur à Chypre, au Liban et dans la majeure partie d'Israel, s'est montré un vecteur important à Jérusalem où elle se multiplie dans les citernes et où, faute d'animaux disponibles elle est devenue strictement anthro pophile. Les tendances exophiles d'*A. claviger* le mettent suffisamment à l'abri du house-spraying pour qu'il soit nécessaire d'avoir recours à lutte antilarvaire pour arrêter la transmission (Gramiccia).

En Malaisie, sauf sur le littoral, *A. maculatus* Theo. est le vecteur principal. C'est pratiquement le seul anophèle attaquant l'homme à l'intérieur des habitations. Il est très exophile et va se réfugier à l'extérieur peu de temps après s'être gorgé. Il manifeste une zoophilie prononcée, 20 % seulement des repas de sang étant pris sur l'homme (Wharton). De ce fait son indice sporozoïtique naturel est très faible, de l'ordre de 0,1 à 0,2 %. Le traitement des habitations au DDT ou au dieldrin réduit faiblement l'agressivité à l'intérieur des maisons, probablement parce que les femelles venant de l'extérieur ne se posent pas, ou peu, sur les murs avant de piquer, mais il entraine une mortalité assez élevée (Reid et Wharton), *A. maculatus* étant très sensible aux insecticides. Dans les zones expérimentales soumises deux fois par an au house-spraying le DDT semble avoir réduit 9 fois la densité anophélienne aux environs des villages, alors que le HCH entraîne seulement une réduction de 3 fois. Dans les deux cas la transmission continue, mais avec trois fois moins de primoinfections que dans les zones voisines non traitées (Edeson et coll.).

A. minimus minimus au Nord Bengale et en Assam est une espèce domestique, endophile, tandis que dans les autres régions de l'Inde (Jeypore Hills) ainsi qu'en Chine, on l'a trouvé à l'extérieur dans les anfractuosités des rochers. En Assam, la réduction considérable de l'infectivité de ce moustique a été obtenue par les pulvérisations au pyrèthre en 1941 (Viswanathan). L'institution des pulvérisations au DDT et à l'HCH dans le Nord du Bengale et en Assam a amené la quasi disparition du paludisme dans ces régions et a ainsi donné la peuve indirecte de l'endophilie de cette espèce dans les régions précitées.

Les recherches préliminaires faites sur *A. minimus flavirostris* aux Iles Philippines par Smith et Dy (1949) ont indiqué que le paludisme transmis par cette espèce ne pourrait être jugulé qu'avec beaucoup de difficulté à cause du degré élevé de son exophilie et de son exophagie. On a trouvé ensuite au cours du projet pilote de Mindoro que les pulvérisations de DDT donnaient des résultats extrêmement satisfaisants. Ceci est probablement dû au fait que *A. minimus flavirostris* a une brève phase d'endophilie durant son cycle gonotrophique et la sensibilité de ce moustique aux insecticides est tellement élevée que se longévité moyenne peut être abaissée à un niveau où le potential de transmission devient négligeable.

A Sarawak *A. leucosphyrus leucosphyrus* Dönitz est le principal vecteur. C'est une espèce nocturne, très exophile, les femelles entrant dans les maisons peu avant de piquer, ne se possant sur les murs qu'un temps bref avant et après le repas de sang, et étant toutes sorties à l'aube. Cet anophèle semble très anthropophile au voisinage des habitations. piquant l'homme de préférence aux divers animaux domestiques, mais il doit être en réalité largement zoophile puisqu'il est très abondant dans la forêt. loin de toute habitation humaine (Colless). Son indice sporozoïtique naturel assez faible (0,4 %) est peut être aussi le reflet d'une vie moyenne assez courte. Le house-spraying ne sèmble pas avoir modifié la densité anophélienne, mais la transmission a été stoppée, malgré la présence au milieu des rizières de huttes de culture où les habitants passent la nuit et dans lesquelles les conditions sont bien plus favorables à la transmission que dans les villages (De Zulueta). Dans le Nord Bornéo le vecteur est *A. leucosphyrus balabacensis* Baisas, dont l'écologie semble sensiblement identique à celle d'*A. leucosphyrus leucosphyrus*, mais qui doit avoir soit une vie moyenne plus longue, soit une anthropophilie plus marquée, car ses indices sporozoïtiques sont 4 à 6 fois plus élevés (Colless, MacArthur). Il est possible que du fait de ces particularités le contrôle du paludisme soit plus difficile à obtenir dans le Nord Bornéo.

En Nouvelle Guinée Hollandaise Metselaar a fait une étude très complète des vecteurs, tous appartenant au groupe *punctulatus: A. punctulatus* Dönitz, *A. farauti* Laveran et *A. koliensis* Owen. Ce sont des espèces nocturnes, exophiles, mais assez anthropophiles. Les femelles-récoltées aux environs des habitations étaient gorgées de sang humain dans les proportions suivantes: *punctulatus* 85 %, *farauti* 75 %, *koliensis* 60 %, alors que les indices sporozoïtiques respectifs de ces espèces étaient de 1,4 %-1,5 % et 1,1 %. Les trois espèces piquent plus volontiers à l'extérieur qu'à l'intérieur, mais sont bien obligées d'entrer dans les maisons pour piquer l'homme car celui ci ne se trouve guère à l'extérieur pendant la nuit. Les femelles à jeun venant de la jungle se posent assez longtemps sur les murs avant de piquer, jusqu'à 110 minutes, et une fois gorgées s'y posent de nouveau un temps plus court avant de ressortir, un faible pourcentage y restant même pendant le jour.

En comparant pour les trois espèces réunies les indices sporozoïtiques des femelles attaquant à l'extérieur au crépuscule et ceux des femelles prises au repos le jour dans les habitations Metselaar a constaté que ces indices étaient significativement différents: 0,18 ± 0,18 % dans le premier cas et 1,3 ± 0,25 % dans le second. Cela traduit probablement une différence de la composition de la population anophélienne, les femelles piquant au début de la nuit étant en majorité jeunes, alors que les femelles agées piquent plus tard et constituent la majorité de celles prises au repos le jour dans les habitations. Ces observations posent un problème d'échantillonnage très sérieux qui n'est peut être pas le monopole de *punctulatus*. Par contre les indices sporozoïtiques des femelles piquant durant toute la nuit et de celles au repos le jour dans les maisons, étudiés lors d'autres recherches, étaient tout à fait comparables: 1,6 ± 0,6 % dans le premier cas, et 1,1 ± 0,8 % dans le second.

Dans des cases expérimentales munies de trappes de sortie Metselaar a obtenu en moyenne, pendant plus de six mois, une mortalité de l'ordre de 75 % chez les femelles entrées dans ces cases traitées au DDT, 65 à 80 % d'entre elles s'étant gorgées malgré la présence de l'insecticide. Il en a déduit que dans une campagne généralisée de house--spraying au DDT la mortalité quotidienne moyenne passerait de 20 à 45 % environ. Or à la suite d'une telle campagne les indices sporozoïtiques du groupe *punctulatus* sont passés dans la zone traité de 0,81 ± 0,36 à 0,28 ± 0,14%, ce qui révèle seulement une légère augmentation de la mortalité quotidienne moyenne qui a du passer de 20 à 25 %

environ. Cela montre combien il est difficile de prévoir à l'aide d'études faites dans des cases expérimentales les répercussions sur le terrain d'une campagne de house-spraying. Metselaar a conclu que dans les conditions locales l'arrêt de la transmission ne pouvait pas être obtenu avec le DDT, mais que les perspectives seraient meilleures avec le dieldrin.

Dans la région éthiopienne les principales études portent sur les deux grands vecteurs, *A. funestus* Giles et *A. gambiae* Giles.

A. funestus est généralement très endophile et très anthropophile, et sa sensibilité aux insecticides est très grande. Le house-spraying l'a éradiqué de l'Ile Maurice (Dowling) et des Hauts Plateaux de Madagascar (Grjebine) et l'a presque fait disparaître du Swaziland (Mastbaum) et de la région forestière de Yaoundé, au Cameroun (Adam).

Dans le South Pare, au Tanganyika, *A. funestus* est très peu exophile, 95 % des femelles restant dans les maisons au moins 24 heures après avoir pris leur repas de sang. Il a peu tendance à piquer l'homme à l'extérieur des habitations et est très anthropophile, 5 à 10 % seulement des repas de sang étant pris sur les animaux sauvages ou le bétail. Son taux de survie quotidien moyen est de 80 % environ. Dans ces conditions le house-spraying avec du dieldrin a entraîné une raréfaction considérable d'*A. funestus,* et son remplacement dans les refuges extérieurs par *A. rivulorum* Leeson, qui était peu abondant auparavant et qui ne joue aucun role dans la transmission (Gillies, Draper et Smith).

A. funestus en Nigeria du Nord présente un degré de zoophilie et d'exophilie plus important que l'on ne s'y attendait en se basant sur les observations faites dans d'autres parties d'Afrique.

Dans la savane soudanaise de Haute Volta, *A. funestus* est assez exophile en saison des pluies et très endophile en saison sèche. Il pique très volontiers à l'extérieur toute la nuit, et les indices sporozoïtiques des femelles piquant la nuit à l'extérieur, piquant la nuit à l'intérieur, et prises au repos le jour dans les habitations, sont tout à fait comparables, étant respectivement de 2,13 ± 0,41 %-1,20 ± 0,33 % et de 1,22 0,23 %. Par contre les femelles attaquant au début et à la fin de la nuit ont un indice sporozoïtique significativement plus bas que celui des femelles piquant au milieu de la nuit: 0,84 ± 0,34 % dans le premier cas, et 2,07 ± 0,36 % dans le second, ce qui traduit probablement une différence d'age moyen des femelles attaquant aux différentes heures de la nuit. L'anthropophilie de cette espèce est très marquée, 75 à 98 % des repas de sang étant pris sur l'homme. Contrairement à ce qui s'est passé au Tanganyika le traitment des habitations au DDT n'a pas entrainé de raréfaction spectaculaire de l'espèce, mais son anthropophilie a considérablement diminuém 15 % seulement des repas de sang étant pris sur l'homme, et sa tendance à l'exophagie a considérablement augmenté. Pratiquement cette espèce ne joue plus qu'un role négligeable dans la transmission, son indice sporozoïtique étant passé de 1,85 à 0,06 %, l'influence de la déviation zoophile étant probablement aussi grande que celle de la diminution du taux de survie qui semble être passé de 90 % à 80 %. *A. leesoni* Evans et *A. rivulorum*, qui sont rares dans la région, ne manifestent aucune tendance à se substiture à *A. funestus* (Hamon, Choumara et coll.).

La situation d'*A. gambiae* est très complèxe. On connait déja toute une série de formes à exigences écologiques différentes: *A. gambiae gambiae* du continent africain, *A. gambiae melas* Theo. des zones saumâtres de la côte occidentale d'Afrique, *A. gambiae litoralis* Halcrow des eaux salées de l'Ile Maurice, ainsi que les formes non dénommées, d'eau saumâtre d'Afrique orientale décrite par Muirhead Thomson, et d'eau douce à oeufs du type *melas* décrite d'Ibadan, Nigeria par Bruce-Chwatt et Service.

A. gambiae gambiae à lui seul présente des comportements très variés, allant de l'endophilie et de l'anthropophilie totale observée dans certains villages de la région d'Enugu, en Nigeria, où les larves vivent dans les jarres constituant les réserves d'eau potable des habitants (Bruce-Chwatt), à l'exophilie et à la zoophilie complète rencontrée dans la Forêt de Bwamba, en Uganda (Haddow).

Les études récentes ont montré que les femelles attaquant aux différentes heures de la nuit étaient également réparties entre les différents groupes d'âges, au Tanganyika (Gilles) comme en Haute Volta (Hamon, Choumara et coll.), et que les femelles attaquant à l'intérieur des habitations, celles attaquant à l'extérieur, et celles prises au repos le jour dans les maisons avaient le même indice sporozoïtique moyen (Fox au Liberia, Hamon, Choumara et coll. en Haute Volta). Il n'y a donc pas lieu de penser que ces différences de comportement correspondent à des races biologiques différentes.

Les répercussions des campagnes de house-spraying varient beaucoup avec les territoires. Dans le South Pare, au Tanganyika, où *A. gambiae* était très endophile, bien que largement zoophile, 15 à 60 % des femelles se gorgeant sur le bétail, les aspersions de dieldrin ont arrêté la transmission, et la densité anophélienne a considérablement diminué (Gillies, Draper et Smith). Dans la zone forestière de Yaoundé, au Cameroun, où *A. gambiae* est largement exophile, mais fortement anthropophile, les aspersions ont également entrainé une raréfaction considérable de l'espèce et arrêté la transmission (Adam, Mouchet et Gariou).

Dans la savane soudanaise de Haute Volta *A. gambiae* est assez exophile en saison des pluies, mais fortement anthropophile, 82 à 99 % des femelles gorgées s'étant nourries sur l'homme. Les aspersions de DDT ont augmenté ses tendances à l'exophagie, mais ne semblent pas avoir entrainé de déviation zoophile, et les indices sporozoïtiques sont passés de $3{,}0 \pm 0{,}3\,\%$ à $0{,}24 \pm 0{,}14\,\%$, la transmission du paludisme n'étant pas interrompue. La souche résistante au dieldrin semble avoir exactement le même comportement et les mêmes capacités de transmission que la souche sensible vivant dans les villages non traités (Hamon, Choumara et coll.).

Au Nord Nigeria, dans le projet du Sokoto Occidental, les recherches effectuées ces quatre dernières années ont montré qu'*A. gambiae* est principalement endophage et endophile, quoiqu'il manifeste une certaine exophagie et exophilie pendant la saison des pluies. *A. gambiae* du Nord Nigeria n'est pas obligatoirement anthropophile. Cette espèce se nourrit souvent sur le bétail et surtout sur les chevaux dans le étables (Bruce-Chwatt et Archibald).

A Madagascar (Lacan), à l'Ile Maurice (Halcrow), au Swaziland (Mastbaum) et en Rhodésie du Sud (Alves), les campagnes d'aspersions auraient rendu *A. gambiae* principalement zoophile, mais il y a eu peu d'enquêtes menées sur ce sujet avec des moyens similaires avant le house-spraying, et des observations récentes, faites à l'Ile Maurice (Hamon) et en Rhodésie du Sud (Ramsdale), laissent penser que cette zoophilie est beaucoup moins grande qu'on ne l'avait cru tout d'abord, et qu'à l'Ile Maurice tout au moins la principale cause de la non infection d'*A. gambiae* est la raréfaction des porteurs de gamètes.

L'ensemble de ces faits montre qu'il est très difficile de prévoir à l'avance le résultat d'une campagne antipaludique basée sur le house-spraying. Des espèces ayant au départ un comportement apparemment identique, voire la même espèce en des points différents de son aire de répartition, se comportent différemment devant les aspersions d'insecticides. La zoophilie comme l'exophilie tantôt facilitent une lutte efficace contre le vecteur, tantôt lui permettent de continuer à transmettre le paludisme en dépit des pulvérisations. Dans plusieurs cas la destruction des gites larvaires s'est avérée la seule méthode de lutte efficace, et dans certaines parties de l'Afrique, de l'Indomalaisie et de l'Australasie, où la lutte antilarvaire ne peut pas être économiquement envisagée, il est probable que les insecticides actuels à eux seuls ne permettront pas d'interrompre la transmission.

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RÉSUMÉ

L'auteur étudie successivement l'écologie de quelques vecteurs importants des différentes parties du monde et leur comportement devant le house-spraying.

Dans le cas des *Kerteszia,* diurnes, anthropophiles et relativement endophiles à l'origine, seule la destruction des broméliacées épiphytes servant de gites larvaires assure un arrêt de la transmission, ces anophèles étant devenus exophiles tout en continuant à piquer l'homme.

Chez des espèces exophiles et zoophiles, comme *A. aquasalis, A. albimanus, A. leucosphyrus leucosphyrus* et *A. maculatus,* dont les indices sporozoïtiques naturels sont faibles, et qui ne sont vecteurs que du fait de leur grand nombre, l'emploi du house-spraying a arrêté la transmission due aux trois premières espèces, apparemment en accentuant leur exophilie et leur zoophilie, mais n'a pu permettre un contrôle efficace de la quatrième.

Chez des espèces exophiles, mais assez anthropophiles, comme *A. punctulatus, A. koliensis, A. farauti* et *A. sergenti,* les aspersions d'insecticides n'ont pas arrêté la transmission du paludisme, sauf pour la dernière espèce dans les zones où ses refuges naturels n'existent pas.

Chez des anophèles assez fortement endophiles et anthropophiles comme *A. labranchiae, A. darlingi, A. funestus* et *A. gambiae,* le house-spraying a arrêté la transmission dans la majorité des cas en amenant leur éradication, ou leur raréfaction ou en accroissant leur exophilie et leur zoophilie, mais n'a pas partout permis le controle de la quatrième espèce qui en certaines zones continue à transmettre et est devenue exophile.

La plupart des espèces ont d'ailleurs un comportement différent d'une région à l'autre de leur aire de répartition, ce qui influe à la fois sur leur role vecteur et sur leur réaction au house-spraying, un très bon exemple étant celui d'*A. claviger* qui n'était un vecteur important qu'à Jérusalem.

En général les caractéristiques écologiques observées avant l'emploi des insecticides lors de campagnes étendues ne permettent pas de prévoir à coup sur l'efficacité de ces campagnes et des études ultérieures sont indispensables.

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 292-302, 1959

PROBLEMS OF MOSQUITO SYSTEMATICS IN THE LIGHT OF MODERN GENETICS

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Recent work on mosquito genetics has been well reviewed by Kitzmiller (1) and Rozeboom (2). This is not attempted in the present paper which is concerned solely to point out certain fundamental similarities between the problems confronting the taxonomist and those arising in connection with mosquito control and the epidemiology of the mosquito-borne diseases. Genetical work on this group has hitherto been scanty and lacking in coordination. The latter defect is shared by mosquito work as a whole since, not surprisingly, the amount of ad hoc research has been large in proportion to that of a more fundamental nature. It is suggested that a proper appreciation of the genetical implications of mosquito problems in general could lead to a more unified approach.

The taxonomist's approach is threefold. Most people would probably say that his first obligation is the provision of an unambiguous name for each taxonomic unit which he recognises. Freedom from ambiguity is achieved by attaching the name to a single specimen of the particular unit, which, for purposes of discussion, may be taken to be a species. This specimen then becomes the type of the species in question. It has only recently become obligatory to designate a unique type in this fashion and much time is currently being spent in choosing lectotypes for older species previously represented either by no type at all or by a series of cotypes.

In principle this procedure offers the best chance of creating an unambiguous system of reference since nothing can be less ambiguous than a single specimen. In practise, however, difficulties of interpretation arise and the reason for this is a genetical one. It is that, in nature, the species is a large, genetically diverse population and it cannot therefore be represented except in part by a single specimen. The same genetical complexity of natural populations lies at the bottom of many problems of epidemiology and control.

The second type of approach made by the taxonomist is synthetic and consists in grouping his species into larger units such as genera, subgenera and species groups. Such groups are commonly regarded as categories of convenience but this does not absolve the taxonomists from trying to make them express as faithfully as possible the true phylogenetic relationships of the species involved. An unnatural category is unlikely in the long run to be anything but inconvenient. Work of this kind is essential if we are to maintain a unified and integrated view of the group as a whole. Because it has been somewhat neglected by mosquito taxonomists in the past it currently consumes a disproportionately large amount of the taxonomic man hours which are available. This is, however, a transitory phase.

The third approach involves the analysis of species into smaller infraspecific units. The most important of these is the subspecies and it is at this level that the taxonomist sees the best chance of attaining true objectivity. Species are kept separate from one another, in nature, by intrinsic reproductive incompatibility while the barriers to gene flow as between subspecies are extrinsic and environmental. Both groups must possess actual limits in nature and it ought, in principle, to be possible to determine these objectively. It is particularly unfortunate that there has been a recent tendency in certain quarters to treat the subspecies as a subjective category of convenience. This has been carried to a point at which authors have, rightly or wrongly, felt themselves to be under pressure from editors of abstracting journals deliberately to falsify the nomenclature used in their papers for convenience of indexing or the like. This is a deplorable state of affairs and cannot be too strongly condemned.

The classical example of the use of the subspecies in anopheline taxonomy is still the analysis of the *Anopheles maculipennis* complex by Bates (3). This pioneer work has been carried further by the cytological studies of Frizzi (4) and other workers (5). Another good example is the work of Colless (6) on the *Anopheles leucosphyrus* complex. Studies such as these are particularly germane to the theme of the present paper because they involve an attempt to understand the organic structure of the groups concerned instead of merely breaking them up into arbitrary units like suspects in an identification parade. There is, however, a great need for more genetical studies if we are to be able to carry this sort of work much further.

Summarising, it would seem that the essential difference between present day taxonomy and that of an earlier vintage is that the present day taxonomist is no longer content merely with the creation of a system of reference. Instead he sees himself confronted with the task of mapping species populations as they actually occur in nature. This is an approach to which no branch of biology can fail usefully to contribute nor in the long run can any aspect of applied biology fail to profit by it.

It has taken us fifty years to learn that if we wish to control the mosquito-borne diseases we must learn to think not like a mosquito but like a population of mosquitoes. One reason that this has taken so long to become apparent is that it is only since the development of the newer insecticides that we have begun to exert on mosquito populations selection pressures greater than those to which they are subjected in nature.

Two main types of response seem so far to have been elicited. Both essentially involve large increases in the relative abundance of previously rare elements in the population, on the one hand individuals abnormally resistant to the action of insecticides and on the other those capable of avoiding such action either through exophily or through some other behavioural idiosyncracy.

Some authors have included both these phenomena under the heading of resistance but this is clearly incorrect. You cannot resist anything by running away from it. Exophily and kindred phenomena should be classed as insecticide avoidance and not resistance. The two phenomena have a quite different significance for epidemiology and control. Geneticists object to the term «acquired resistance» because, in general, nothing new is in fact acquired. All that happens is that there is an increase in the number of resistant individuals from a small to a relatively large proportion of the population. It is, however, arguable that the population, as a population, acquires a greater degree of resistance and it is this which is important from the point of view of control.

It is important to distinguish between the type of resistance developed by populations and the resistance which may be developed by an individual during its lifetime in response to sublethal doses of some chemical. The latter, although it is a true acquired resistance, is perhaps better termed habituation to avoid confusion.

The genetics of resistance have so far been so little studied at the population level that not much more can usefully be said. The observation by Holstein (8) that resistant *Anopheles gambiae* show an unusually high level of cytological variability is interesting. This may play an important part in the hybrid sterility which has been encountered as between resistant and non-resistant strains of this species. If so it provides a good example of the fact that genetical factors need not always operate against us since in this case they serve to prevent the spread of resistance to non-resistant populations. Another interesting study of population structure in relation to insecticide resistance has been that of D'Alessandro *et al.* (5). For further discussion of resistance in mosquitoes the reader is referred to the excellent review by Busvine (7) and to other papers in this symposium.

The subject of exophily is also discussed elsewhere in these proceedings and there have been several recent reviews (9, 10, 11) but reference may perhaps be made to the very interesting studies of insecticide avoidance made by Trapido (12) in Panama. In this case a great reduction in the numbers of *Anopheles albimanus* found in houses was achieved by the use of DDT. Later, however, the numbers again rose to a high level in spite of the presence of the insecticide. This was shown to be the result not resistance but of the development of behavioural changes leading to an avoidance of the insecticide. At the same time, however, the proportion of the population found to be engorged remained at a low level and there was no apparent increase in malaria. This seems to suggest that insecticide avoidance may sometimes be a less serious menace to disease reduction than insecticide resistance since, although it reduces the numbers of insects killed, it may also interrupt the transmission of the disease from insect vector to human host.

Even after a successful reduction or eradication campaign there remains the problem of possible reinfestation. This appears to involve certain factors operating at a still higher level of biological organization than that of the species population. Every species lives in association with other species, both of plants and of animals, with which it is more or less integrated to form a biological whole. Such integrated populations are known as biocenoses and, without pushing the analogy too far, they behave to some extent like the genetically compatible populations which we have seen make up the species. Thus they are capable to some extent of responding to selection pressures by an adjustment of the proportions of their constituent members. It follows from this that if one of these members is eradicated or reduced in numbers one or more of the others will increase and take its place. A particularly good example of this is the apparent replacement of *Anopheles labranchiae* by *Anopheles hispaniola* during the Sardinian campaign (9). This is a factor which could operate powerfully in our favour by delaying or even completely inhibiting reinfestation by a vector species once its numbers have been reduced below a certain level. In this connection there is a great need for quantitative data and a follow up of any eradication campaign would seem to be highly desirable. The factor of competition between species with similar biological requirements is also of fundamental importance in the epidemiology of the zoonoses. Thus is appears that the important vector *Aëdes albopictus* has been kept ou of East Africa largely if not entirely by its inability to compete with *Aëdes aegypti* (13) while the relatively slow spread of the latter into the oriental region during the present century has been due to the necessity of supplanting *Aëdes albopictus* and other established species (14).

The future outlook in the mosquito-borne diseases is obscure but one thing seems clear. Whether we have to deal with resistance or with residual populations or reinfestation or behavioural change we shall inevitably have to adopt a more sophisticated attitude to our problems than in the past. Our capacity to understand the nature of these problems will be the measure of our ability to appreciate the potentialities and limitations of the particular level of biological organization with which we have to deal.

As to the particular means by which our knowledge of mosquito genetics may be extended, these must depend on circumstances. Certain considerations of a general kind are, however, perhaps worth emphasising. Thus it is not necessary to rely exclusively on field studies of population genetics, desirable though these undoubtedly are. A great deal can be usefully learnt from the cage populations of mosquitoes which are currently maintained as laboratory animals in many parts of the world. Such studies will, in many cases, be well rewarded by the increased efficiency of strains selected for the particular purpose for which they are required.

Again, it is not necessary to rely exclusively on anopheline mosquitoes. We are slowly learning a good deal about culicine genetics. Differences certainly exist but we should not be deterred from trying to understand these and learning to what extent we may safely extrapolate from one group to the other. Far too often in tropical medicine the left hand operates in ignorance of what the right hand is doing.

Nor should we adopt a defeatist attitude, assuming that all genetical factors must necessarily operate to our detriment. Examples have been given of instances in which such factors might well be turned to our advantage. We should always be alert to detect these and exploit them where possible.

Perhaps the most important question of all is that of education. The greatest possible credit is due to those few applied entomologists who have taught themselves the rudiments of genetics and applied these to the study of resistance and the like. Nor should any serious student of medical entomology be allowed to complete his training without being given at least some inkling of the genetical implications of his studies. It is to be doubted, however, whether this alone is enough. It is greatly to be desired that at least a few specialists in genetics should be persuaded to turn their attention from fruit flies to mosquitoes and that some young postgraduate students should be induced to ground themselves in the best possible school of population genetics and then take up the mosquitoes as a suitable group for their further studies.

Finally it should not be forgotten that genetics is itself a rapidly growing science and it is highly desirable that there should be at least a few medical entomologists capable of recognising and exploiting any potentially useful advances which may be made and of communicating with genetical specialists on a reciprocal basis.

We live in a world which has suddenly been made aware of genetical hazards which it has previously been convenient to ignore. Nor are the most dramatic of these necessarily the most potent. In the newer insecticides, just as in atomic reactors or therapeutic X-rays, man has become possessed of biological agents more powerful than any he has had before. All these hazards equally demand a more profound knowledge of fundamental genetics. Is it too much to hope that those who are now engaged in promoting genetical changes in mosquito populations on an unprecedented scale may be able to contribute in some measure to this wider understanding?

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THE IMPORTANCE OF INSECTICIDE-RESISTANCE IN THE FIGHT AGAINST MALARIA

Dr. JAMES R. BUSVINE

National anti-malarial campaigns covering large areas of tropical countries have become commonplace and now, under the aegis of the World Health Organization, these are being coordinated into a world-wide eradication programme. It is no exaggeration to say that this could not have been visualised without the new synthetic insecticides. It therefore follows that the most serious threat to realisation of these ambitious plans is the emergence of insecticide resistant strains of mosquitoes. In our present state of knowledge, it is impossible to forecast whether this trouble will eventually arise in every species which is attacked with insecticide on a sufficiently wide scale and for a long time. In any case, since the risk is always present, the chances of successful malaria eradication must depend on many imponderables, calling for throughness and precision based on a clearer understanding of the nature of resistance. Apart from the necessity of dispelling ignorance, it is important to expose misleading analogies between resistance of insects, drug resistance in bacteria and disease immunity in higher animals. The essential characteristic of resistance in insects is that it is not acquired by individuals as a result of sub-lethal exposure to the poison (The evidence suggests that sub-lethal treatments actually increase the susceptibility of insects to subsequent doses). Resistance is clearly a genotypic character, which tends to supplant the normal type, which is more easily killed by insecticide. So far as we are able to judge, the genes responsible for resistance are pre-existing in certain populations and are merely concentrated by selective mortality. There is no evidence that the insecticide itself stimulates the appropriate mutations, which would indeed be contrary to general experience (at least in the metazoa).

It has been tacitly assumed, in the foregoing paragraph, that resistance is due to a single gene (or a small number of them). This

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 310-316, 1959

seems to be true of the more serious type of resistance which protects the insect from a particular type of poison. Specific resistance of this kind is described as «true physiological resistance». It gives higher levels of immunity than the generally reduced susceptibility to all kinds of poison known as «vigour tolerance». Another term commonly used is «behaviouristic resistance», intended to describe strains of insects with changed reactions affecting their behaviour. The evidence for the existence of such strains is tenuous. The increased exophily of some mosquitoes following DDT spraying does not necessarily constitute behaviouristic resistance, since this is a natural reaction, characteristic of some normal mosquitoes.

DETECTING AND MEASURING RESISTANCE

Investigations of resistance, either in the field or in the laboratory, are handicapped by several difficulties. The character under investigation is invisible and can only be assessed by killing groups of mosquitoes and deducing the levels of resistance in a population, by the quantal response method. Another difficulty is that resistance is not an absolute, but a relative character. It is, therefore, essential to have precise and reliable methods of measuring it. Since the relative difference between normal and resistant insects depends on the method used, it is most important for all workers to employ the same techniques; otherwise a particular level of resistance will appear seriously high by one method and of small magnitude according to another. Lastly, it is important for a test method to be simple enough for field use. Considering these problems, it is very satisfactory to observe that methods for international use are being approved by the World Health Organization. Techniques suitable for adult and for larval mosquitoes have been in use for some time; and a considerable body of data is accumulated on susceptibility levels of malaria vectors in different countries.

Insects in general, and mosquitoes in particular, are very variable physiologically. Their metabolic rate (which governs susceptibility to insecticides) may change from hour to hour in response to temperature and it may undergo slower but more profound changes from season to season. Consequently, there is a wide range of variation of susceptibility in normal mosquitoes which must be discounted, before the existence of an (abnormal) resistant strain is established. Mosquitoes in temperate regions, for example, show a natural decline in susceptibility at the onset of hibernation in autumn.

GENETICS OF RESISTANCE IN MOSQUITOES

The problems of detecting and measuring resistance add greatly to the difficulties of genetical investigations of this phenomenon. In many of the earlier investigations on the inheritance of DDT-resistance in *Musca domestica,* the techniques were inadequate and the results formed a welter of confusion. So far as the housefly was concerned, Dr. R. Milani has pointed out that most of the investigators, who relied upon discriminating doses to assess segregation, concluded that resistance depended on a single gene; whereas workers relying on the shape of probit/dose curves, generally considered that the inheritance was multifactorial.

So far, the genetics of resistance of two anopheline mosquitoes have been elucidated, by Mr. G. Davidson of the Ross Institute, London. Both followed normal Mendelian patterns for single gene inheritance. Experiments with the dieldrin-resistant *Anopheles gambiae* from N. Nigeria, were complicated by a high degree of sterility in male progeny of the first cross. Nevertheless, the results clearly established that the resistant gene was partially dominant, so that the hybrids were intermediate in resistance between the two parents. The other anopheline investigated was a DDT-resistant strain of *A. sundaicus* from Java, which was crossed with a susceptible strain from Malaya; this work proved the resistance factor to be recessive. A practical consequence to be expected when resistance is recessive, is that selective mortality will not foster the resistant strain so rapidly (at least in the early stages) because the hybrids will be killed as easily as the susceptible parents.

The stability of resistance in the absence of the relevant insecticide (e. g. after changing to a different type of insecticide) is of considerable practical importance. Much will depend on whether other biological characters of positive or negative survival value, are linked to the resistance in some way. Theoretically, one would expect such characters to be deleterious, since this would explain the original scarcity of resistant individuals before insecticide is used. Curiously enough, however, resistant colonies of *A. gambiae* and *A. sundaicus* seem to be more vigorous than normal ones, at least in the laboratory. Resistant houseflies appear to be somewhat less viable than normal, since they slowly become scarcer in mixed colonies not subjected to insecticidal treatment. In the field, too, DDT-resistant houseflies tended to become rarer when that insecticide has been abandoned; but they soon become dominant when DDT is re-introduced (at least within 3 to 4 years). So far, indeed, we must admit that when resistance has developed to a particular type of insecticide, that method of control is virtually lost, for an indefinite period.

BIOCHEMISTRY OF RESISTANCE

One reason for our failure to combat resistance is our ignorance of the biochemical mechanisms involved (which extends even to the original mode of action of most insecticides). The first step should be to classify the different kinds of physiological resistance which have been observed. Broadly speaking, the 3 main types involve the following groups of insecticide: (i) DDT and similar compounds; (ii) *gamma* BHC and the cyclodiene compounds such as chlordane and dieldrin; (iii) organo-phosphorus compounds. These three main groups are quite independent, so that resistance to DDT does not involve *gamma* BHC, and *vice-versa*. But within the groups there is generally more or less cross resistance, so that resistance to *gamma* BHC will evoke some tolerance of dieldrin (and *vice-versa*).

The next step is to analyse the 3 main types further, to see whether they comprise one entity or many. This can be done by working out «resistance spectra», i. e. the pattern of relative degrees of resistance shown to a group of related compounds, by a given resistant strain. Some progress has been made in this direction for there is evidence of considerable consistency in type (ii) resistance, as exhibited by *Anopheles gambiae, Cimex lectularius* and *Musca domestica,* suggesting a common mechanism to cope with this group of poisons, possessed by three very different insects (Fig. 1). On the other hand, resistance spectra for the DDT group differ in strains as well as between species of insects. Probably DDT-resistance depends on more than one protective mechanism. The best known factor (clearly very important) is the

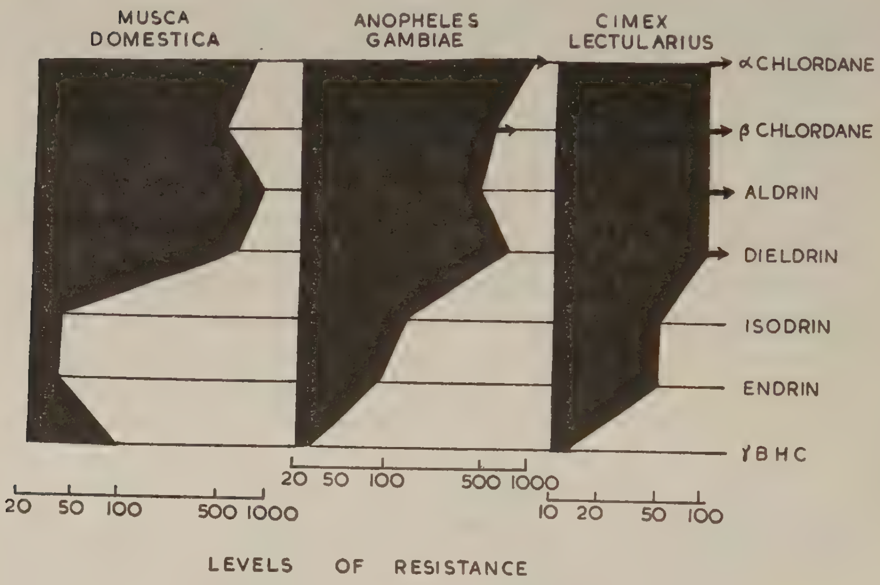

Fig. 1 — «Resistance Spectra» of strains of three different species showing resistance to the BHC-chlordane group of insecticides

detoxication of DDT by a dehydrohalogenating enzyme, first demonstrated by C. Kearns and his team in Illinois. Recent work in Switzerland, by Wiesmann and colleagues, suggests that the type and distribution of lipids in the bodies of resistant houseflies are important.

Strictly biochemical investigations of the other two types of resistance have not yet proceeded very far. Detoxication of *gamma* BHC (and recently of a sulphur analogue of dieldrin) have been demonstrated in resistant houseflies, by a process quite distinct from the dehydrochlorination of DDT. Another kind of resistant strain, resistant to organo-phosphorus compounds, appears to detoxify paraoxon. It is not entirely established, however, that the detoxication mechanisms in these cases are the sole cause of resistance. Attempts to demonstrate enhanced degradation of *gamma* BHC by resistant *Anopheles gambiae* have been unsuccessful.

FUTURE POLICY OF ANTI-MALARIA SCHEMES

In considering policies to be adopted in view of potential resistance, a number of disagreeable facts must be squarely faced. Firstly, although resistance may not be inevitable, it should be assumed that any large and prolonged insecticide campaign may eventually induce it. Secondly, it must be realised that no practical solution to resistance has yet been found, other than changing to an alternative insecticide. This is far from satisfactory, because the number of types of insecticide available is small. An insect which has become seriously resistant to both DDT and *gamma* BHC, is likely to be virtually immune to all the new chlorinated synthetic insecticides. A third depressing fact is that resistance seems to develop most quickly and to highest levels towards the most persistent insecticides. Unless this is a remarkable coincidence, it follows that any insecticide, with the valuable property of long residual action, is liable to induce resistance.

In trying to devise ways of using insecticides without provoking resistance, we are still handicapped by limitations of our fundamental knowledge. Thus, one possible solution, which appears to be quite practical, is a combined attack by insecticides of different types. This could be in the form of a mixture, or by alternation, or by separate use on adult and larval stages. The exact effects of such combinations on the chances of inducing resistance, depend on several factors which are not yet fully understood. They include (i) the degree in correlation in susceptibility to the two types of poison, shown by the insect population; (ii) the genetic mechanisms involved; (iii) the proportions of the population effectively reached by insecticide and the length of the exposure in relation to the life cycle. It is evident that some of these questions must be studied in the laboratory and some in the field. But the results of field trials will give the ultimate answer; and since they will take several years, it is very desirable to begin trials of the more promising combinations of insecticides (as far as we can judge now) as soon as possible.

Apart from these suggestions, the only policy likely to be helpful is to employ the greatest discretion in any large-scale use of insecticides. A most unsatisfactory situation would exist if sporadic minor insecticide campaigns, undertaken by public health services, were allowed to induce resistance without eliminating disease. This would be especially regrettable, if a properly planned campaign would have been able to secure disease eradication. Malaria control schemes should be reviewed in this light and should be replaced with a definite eradication plan, wherever this is feasible.

Before any malaria eradication campaign is started, the level of susceptibility of the vector should be measured (by a method approved by W. H. O.) if this has not already been done. Subsequently, a careful watch for signs of resistance should be maintained, and plans for coping with it prepared. One obvious plan would be to switch to an alternative insecticide. Another, which would be helpful if resistance comes in the later stages of a campaign, would be to mop up the last pockets of the disease by the systematic administration of drugs.

MALARIOMETRIC EVIDENCE FOR DDT RESISTANCE IN *ANOPHELES STEPHENSI* IN OASES OF EASTERN SAUDI ARABIA

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The occurrence of insecticide resistance in major malaria vectors is of great concern to malariologists throughout the world at the present time. Reports of DDT resistance in *Anopheles stephensi* in the Persian Gulf areas of Saudi Arabia, Iraq, Iran and in India, in *A. sacharovi* in Lebanon and Greece, and in *A. sundaicus* in Java and Burma have been well publicized. Additional reports of possible DDT resistance in *A. maculipennis* and in *A. superpictus* have also come from Greece. Dieldrin resistance has been reported in *Anopheles gambiae* in Africa and in *A. quadrimaculatus* in the United States. More recent reports indicate that other anophelines, less important as vectors, are also developing resistance to the commonly used residual insecticides.

In most of these cases, reports of insecticide resistance are primarily entomological, and few accounts have been published to emphasize the importance of the problem as far as direct effects on malaria control are concerned. The present paper is intended to present malariometric evidence for DDT resistance and resumption of effective control when dieldrin was substituted for DDT. Evidence from morbidity data in adults and parasite rates in village children will be presented to show (1) the initial sucess of DDT in controlling *stephensi* — transmitted malaria, (2) subsequent failure of control programs due to DDT-resistance, and (3) more recent success in control with dieldrin.

The localities providing these data are the two oases of Qatif and al-Hasa located in eastern Saudi Arabia along the Persian Gulf coast. These two large oases include a population of about 300,000 people scattered in some 80 towns and villages. Malaria had always been a most important health problem in these bases until DDT residual sprays were first used in a cooperative Saudi Arab Government — Aramco (¹) malaria control program in 1948. The entire Qatif oasis was first treated in 1948, the al-Hasa oasis in 1949. With minor exceptions, residual sprays have been applied annually each fall since that time. In 1956, responsability for the spray programs was taken over by the Saudi Arabian Ministry of Health, and they are continuing the programs at present.

Basic pre-control malariometric data are available from morbidity rates in Saudi Arab employees of the Arabian American Oil Company and from malaria surveys in selected villages in the two cases. These data show an annual average of 1,631 cases per 10,000 employees in the pre-control years 1941-1947. A pre-control parasite rate of 85 % was recorded from village children in the Qatif oasis in 1947. The pre-control infant parasite rate in the surveyed villages was 100 %. With the first use of DDT in 1948-1949, both morbidity rates in adults and parasite rates in infants and children began a sharp decline and continued at low levels through 1952. In 1953, a slight increase in both rates occurred; and by 1954, our records show that DDT was obviously failing to control malaria adequately. When dieldrin replaced DDT, control was again resumed. A more detailed analysis and explanation of these trends is given below.

EVIDENCE FROM MORBIDITY RATES

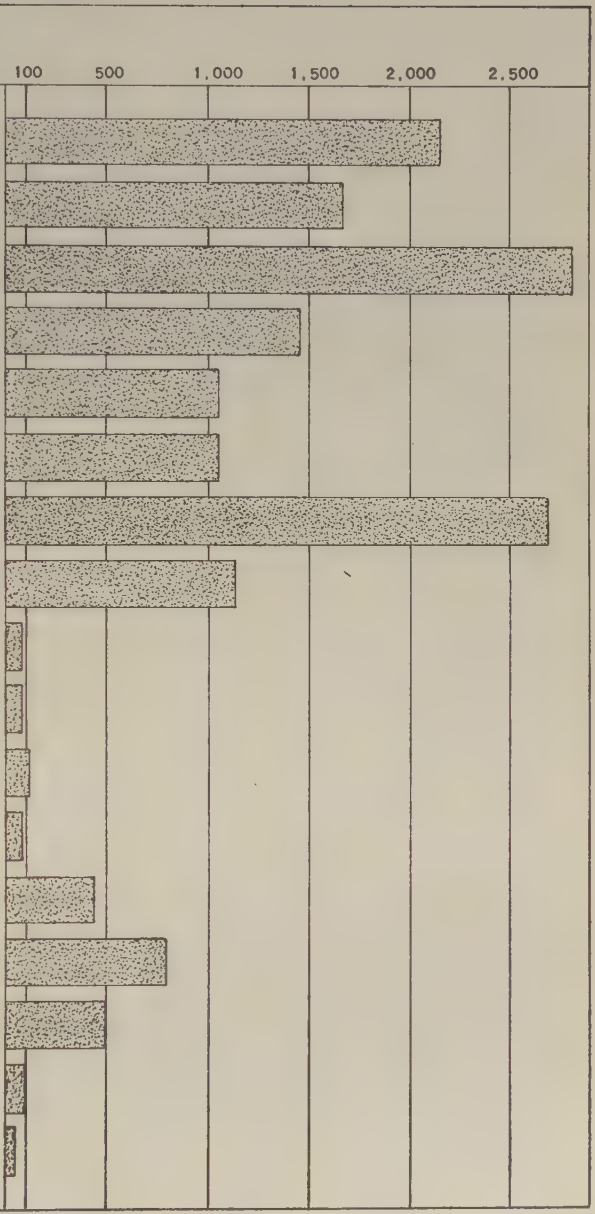
Data on malaria morbidity in Saudi Arab employees of the Arabian American Oil Company are available since 1941 (Fig. 1). The relatively high annual malaria attack rates are evident from 1941-1947. With the first use of DDT in the fall of 1948, annual rates in employees dropped sharply in 1949-1952, ranging from 87-120/10,000 in contrast to the average of 1,631/10,000 in pre-control years.

In retrospect, DDT resistance had probably developed far enough by late 1953 to begin affecting malaria control. In that year, the employee morbidity rate was 422/10,000; and by the end of 1954, a rate of 780/10,000 was unmistakeable evidence of DDT's failure to control malaria adequately.

(¹) Arabian American Oil Company.

FIG. 1 ANNUAL MALARIA MORBIDITY RATES IN ARAMCO SAUDI ARAB EMPLOYEES 1941-1957

YEAR	NUMBER MALARIA CASES	MIDYEAR EMPLOYEE STRENGTH	MORBIDITY RATE PER 10,000
1941	380	1,772	2,144.5
1942	280	1,681	1,665.7
1943	540	1,940	2,783.5
1944	688	4,784	1,438.1
1945	838	8,021	1,044.8
1946	802	7,437	1,078.4
1947	2,101	7,846	2,677.8
1948	1,356	12,000	1,130.0
1949	94	10,828	86.8
1950	95	9,606	98.9
1951	142	11,874	119.6
1952	137	14,298	95.8
1953	589	13,964	421.8
1954	1,077	13,464	799.9
1955	686	13,656	502.3
1956	129	13,261	97.3
1957	54	12,837	42.1



With the first use of dielarin in the fall of 1955, malaria incidence among Aramco employees rapidly declined to previous low levels. More recent applications have brought the 1957 rate to a new low of 42/10,000, and reports for the first half of the present year indicate a much lower figure for 1958.

EVIDENCE FROM MALARIA SURVEYS

Data from malaria surveys in the villages show the same sequence of events (Fig. 2). Two experimental villages in the Qatif oasis — al-Ajam and Safwa — have been surveyed each fall from 1947 through 1957. The original pre-control survey showed a parasite rate of 74 % in the 2-14 year age group. Although infant parasite rates were not determined in these two villages, other similar villages showed a transmission index of 100 % before control attempts began.

With initial use of DDT in these villages in 1948, parasite rates dropped to 13 % in 1949 and to 1 % by 1952. In the fall of 1953, an unexpected increase to 14 % was cause for concern when similar increases were noted in numbers of employee cases reporting to our clinics. Our 1954 fall survey, with its 45 % parasite rate, confirmed the failure of DDT to control malaria as already indicated in our employee morbidity data. Again, in retrospect, this trend probably started in late 1953.

Infant parasite rates dropped from a pre-control 100 % to 0-18 % in 1949-1952. By 1953, they had risen to 28 %, and in 1954 to 31 %. This was additional evidence indicating increasing failure of DDT to check malaria transmission.

With the use of dieldrin in the fall of 1955, parasite rates (including infant parasite rates) again dropped sharply to 4 % in 1956 and to 1 % in 1957. In both of these years, the infant parasite rate was nil indicating complete interruption of transmission. The three positive blood films in these villages in 1957 all showed *malariae* parasites which very probably represent old rather than new infections in 1957. Again, the successful initial control with DDT and later success with dieldrin indicate that the failure of DDT to reduce village parasite rates in 1953-1954 and early 1955 was due to development of DDT-resistance in *Anopheles stephensi*.

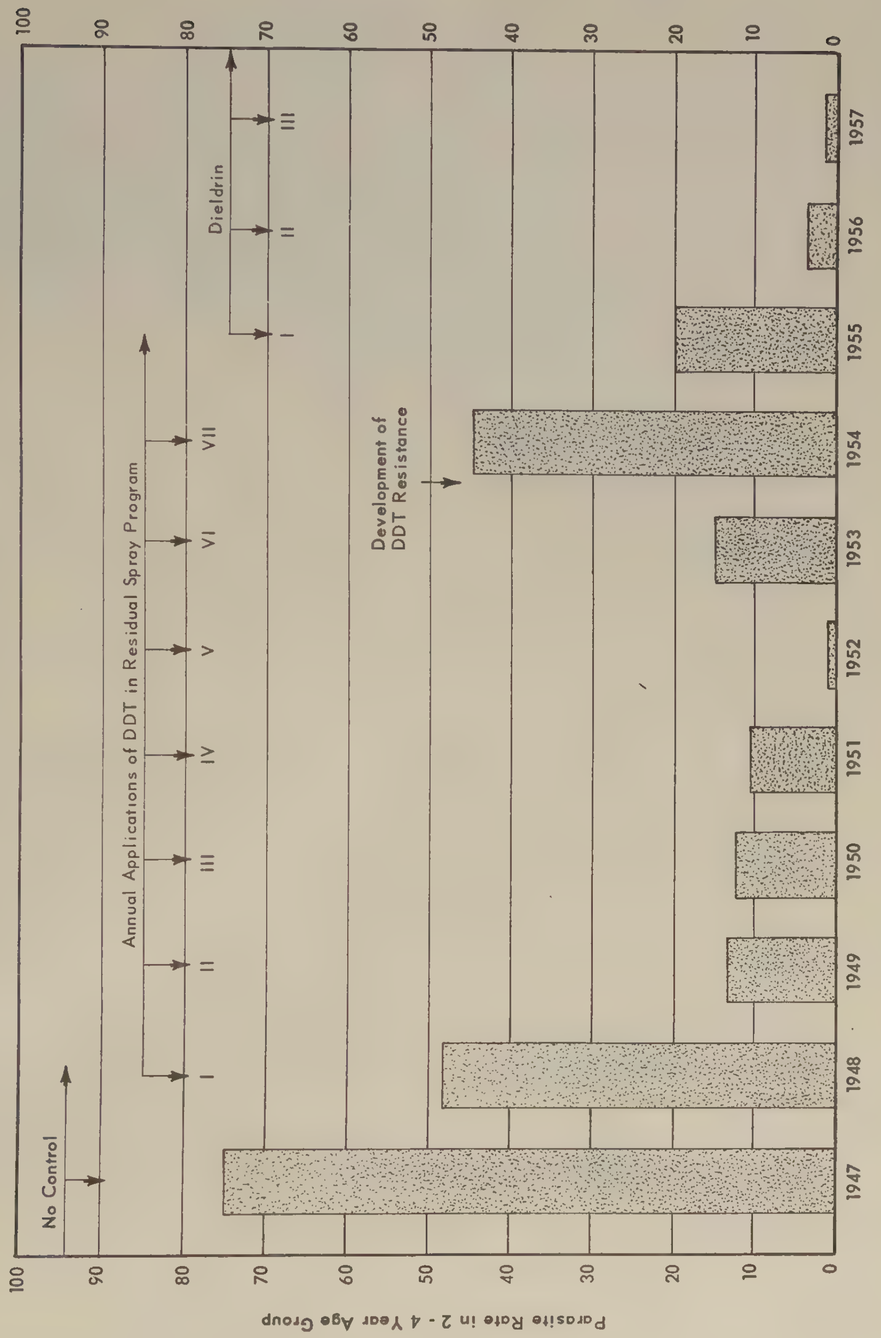


FIG. 2 - DEVELOPMENT OF DDT RESISTANCE AND RESUMPTION OF CONTROL BY DIELDRIN

EXPERIMENTAL QATIF OASIS VILLAGES - AL-AJAM AND SAFWA

1947 - 1957

ENTOMOLOGICAL EVIDENCE

After the first DDT application in 1948, a year elapsed before the first anophelines were found on treated surfaces. But by the fall of 1954, *stephensi* were returning to treated shelters only a few weeks after DDT application. This failure to exclude anophelines paralleled the increase in large numbers of malaria cases both in employees and in the villages. Thus field entomological evidence, as well as malariometric evidence, increased our suspicion of DDT-resistance in *stephensi*. In early 1955, we cabled the World Health Organization at Geneva indicating our belief that DDT-resistance had developed in *Anopheles stephensi* in these oases and that dieldrin would be substituted for DDT in our next fall residual spray program.

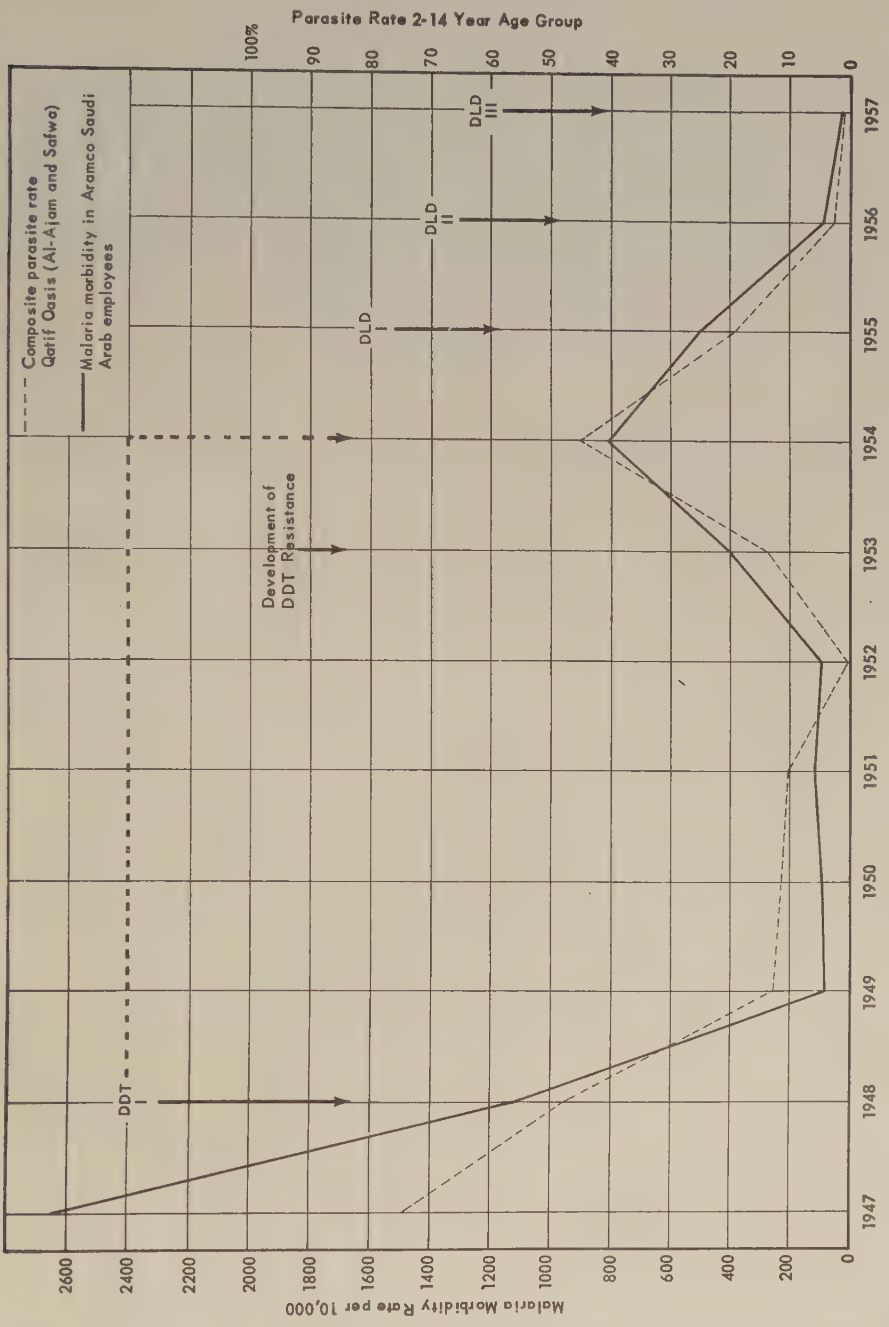
Later in 1955, Mr. George Davidson, W. H. O. Consultant, visited Saudi Arabia in connection with resistance studies. Working with Dr. R. L. Peffly and utilizing the Busvine-Nash technique, a 10-fold difference in resistance to DDT was demonstrated when *stephensi* from treated areas were compared with those from unsprayed check areas. This, added to malariometric and field entomological evidence, confirmed our belief that DDT resistance was responsible for malaria control failure in our oases.

To summarize our malariometric evidence for DDT-resistance in *Anopheles stephensi*, we have plotted malaria morbidity data from Aramco employees along with results of oasis village surveys for the same periods (Fig. 3). Here is excellent parallel evidence of (1) a most serious malaria problem in 1947 before control began, (2) a sharp decline with use of DDT to low levels of infection from 1949-1952, (3) a slight increase in 1953 with developing DDT resistance, (4) marked failure of DDT to control malaria adequately in 1954, and (5) resumption of successful malaria control with dieldrin in 1956 and 1957.

In conclusion, we can point out that our 1958 experience thus far indicates the probability of even lower malaria morbidity rates for this year. *Anopheles stephensi* is now very difficult to find in the dieldrin sprayed areas. If no resistance to dieldrin develops, malaria eradication may be a very realistic goal with use of dieldrin residual sprays alone in these two oases in eastern Saudi Arabia.

FIG. 3 - MALARIOMETRIC EVIDENCE FOR DEVELOPMENT OF DDT RESISTANCE

QATIF OASIS 1947 - 1957



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O SAL DE COZINHA COMO VEÍCULO DE MEDICAMENTOS ANTIMALÁRICOS — SUA IMPORTÂNCIA NOS PROGRAMAS DE ERRADICAÇÃO DA DOENÇA

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I — *Introdução*

O método do «sal cloroquinado» foi imaginado nos fins de 1951, quando logo suspeitámos que com a dose única de cloroquina poderíamos proteger apenas grupos seleccionados de indivíduos, e não populações. No ano seguinte, eram iniciadas as experiências físico-químicas essenciais, assim como o tratamento hospitalar experimental, com malária natural e com malária induzida.

Na época, era a cloroquina o mais eficiente antimalarico conhecido e foi por isso o escolhido. Actualmente usa-se também a pirimetamina (Coatney *et al.*, 1958) e no futuro, com os avanços da moderna quimioterapia, outras drogas ainda mais eficientes serão empregadas na mistura.

Resolvidos os problemas preliminares que permitiram o uso do sal cloroquinado e obtidos os primeiros resultados hospitalares que demonstravam a sua eficiente acção antimalárica, foram iniciadas as experiências de campo. Estas, por sua vez, forneceram resultados ainda mais concludentes. *Era possível eliminar a malária* — em áreas não dedetizadas e na ausência de qualquer outra terapêutica específica — *pelo uso exclusivo do sal de cozinha enriquecido pela cloroquina.*

Portanto, o sal cloroquinado possibilitou, pela primeira vez, *o uso de drogas quimioterápicas para a profilaxia em massa da malária.*

Presentemente, na campanha de erradicação da malária iniciada no Brasil, com a cooperação da I. C. A. e da O. M. S./R. S. P. A., a

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(¹) The author did not attend the meeting.

execução dessa tarefa na região amazónica será feita na base de um vasto plano de distribuição do sal cloroquinado.

II — *O método do sal cloroquinado*

Os testes físico-químicos mostraram que o sal cloroquinado não produz concentrações cumulativas tóxicas após uso prolongado e resiste por longo tempo à cocção em meio de *pH* 4-7, sem que haja alterações do medicamento (1, 3, 4 e 5).

O estudo referente à eliminação da cloroquina através da urina, na qual a sua presença é fàcilmente demonstrável, representa um utilíssimo elemento de *contrôle* do uso do sal cloroquinado no campo. Por outro lado, desenvolveram-se técnicas acuradas para a rápida verificação da cloroquina no sal (9, 18).

Ùltimamente, verificou-se que, em área onde o sal é iodado (combate ao bócio), a adição da cloroquina causou um cheiro desagradável à mistura. Esse inconveniente foi sanado pela adição de tiossulfatos juntamente com a cloroquina. Entretanto, na Amazónia, onde o método do sal cloroquinado tem a sua mais ampla aplicação, o problema do bócio é sem importância, de modo que a iodação do sal será adiada.

Em baixa humidade, o sal cloroquinado mantém-se em boas condições de mistura até por 4 a 6 meses, tanto no laboratório como no campo. Porém, sendo o sal de consumo altamente higroscópico, o seu teor de água eleva-se quando as condições de humidade são muito altas (acima de 80 %). Então, como a cloroquina se dissolve na água, a longa estocagem faz com que a mistura perca a sua uniformidade. Entretanto, este inconveniente não tem interferido com os bons resultados do método no campo (22).

As pesquisas que demonstraram a eficiência do sal cloroquinado como antimalárico foram realizadas sob condições hospitalares (com malária natural e com malária induzida) e no campo (*Plasmodium falciparum, P. vivax* e *P. malariae*) (6, 8, 18).

Nas condições hospitalares, como é óbvio, os resultados foram uniformemente mais favoráveis nos casos de malária induzida (sangue infectado). Mas verificou-se também a eficiência do método na malária natural. Por outro lado, não houve desenvolvimento de resistência à cloroquina por parte dos plasmódios.

Diferentes doses de cloroquina foram experimentadas, sendo considerada melhor para a rotina a de 0.030 g/base (6, 18).

No campo, os resultados ainda foram mais concludentes que sob as condições hospitalares. Foi possível controlar a malária pelo uso do sal cloroquinado, conforme mostraram diversas experiências em áreas de transmissão por diferentes espécies vectoras: no Pará (*A. darlingi*), no Maranhão (*A. tarsimaculatus*) e no Paraná [*A. (K) bellator*] (7, 18).

III — *Exemplos de recentes resultados obtidos no campo*

I) *No território federal do Amapá* — No 1.º semestre de 1957, em área não dedetizada e de transmissão pelo *A. darlingi,* com infecções quase que exclusivas pelo *P. vivax* com apenas 1 mês de uso do sal cloroquinado, viu-se índice parasitário de 60.8 cair para 2.3.

II) *No Estado de Minas Gerais* — Em Engenheiro Dolabela, mesmo com 3 aplicações anuais de D. D. T., continuava certo grau de transmissão (*A. darlingi*). No período de 1950-1954 registou-se uma média anual de 187 casos. Bustamante (10) apontou como responsáveis por essa malária residual não só uma certa transmissão extradomiciliária, como também uma provável «modificação de comportamento do vector». Nessa região, após 2 meses de uso do sal cloroquinado e durante 6 meses (Dezembro de 1956 a Maio de 1957) — justamente na época de recrudescimento da transmissão —, não foi observado nenhum caso de malária.

III) *No Estado de Santa Catarina* — No município de Biguassu, região de Kerteszia (*A. cruzii* e *A. bellator*), ocorria facto semelhante: o D. D. T. não conseguia eliminar a malária residual. De Janeiro a Maio, cada ano, ocorriam 40 a 50 casos de malária. Iniciado o sal cloroquinado em Dezembro de 1956, em todo o primeiro semestre de 1957 só foi observado um caso de malária em lactente.

IV — *Indicações do novo método*

Nos primeiros 6 anos de uso do D. D. T., o objectivo visado era a redução da incidência da malária a níveis satisfatòriamente baixos, isto é, o *contrôle da doença.* Com o correr do tempo, porém, dois importantes factos determinaram uma profunda modificação nessa política profiláctica: *primeiro*, a observação de que em algumas áreas — onde os programas de *contrôle* com D. D. T. foram mais rigorosos ou as condições epidemiológicas eram mais favoráveis — se conseguira não sòmente a queda da transmissão da doença, mas *a sua completa eliminação*; *segundo*, o facto constatado em alguns países, de que os anofelinos transmissores podem, depois de algum tempo, adquirir *resistência ao D. D. T. e a outros insecticidas*. Essas duas verificações determinaram, então, uma nova estratégia na luta contra a malária. Dever-se-ia procurar *obter a erradicação da doença o mais ràpidamente possível*, com a eficiente dedetização e com a procura intensiva de casos, para eliminá-los pela quimioterapia, *antes que as espécies transmissoras pudessem adquirir resistência*.

Com tal orientação, a malária já foi erradicada de grandes áreas de diversos países, e o mesmo poderá ocorrer, provàvelmente, na maior parte das áreas maláricas nos vários continentes. Todavia, *certos factos de ordem epidemiológica, ou de carácter administrativo e económico, tornam muito difícil a erradicação da malária, nas bases propostas*.

Foi principalmente a Amazónia, além de outras regiões do Brasil, que, depois de alguns anos de trabalho, nos levou a *buscar medidas para contornar as dificuldades encontradas pela dedetização domiciliária*. Primeiro, foi o factor económico: enquanto o preço unitário do expurgo nas outras zonas malarígenas era, em média, de Cr $ 80,00, na Amazónia ele era quase 3 vezes maior. *Longas distâncias, acesso difícil e produção muito baixa*. Além disso, tempo e dinheiro eram gastos, na maior parte para atingir os domicílios, pois, muitas vezes *eles não tinham paredes a proteger*. Por outro lado, nos seringais e nos garimpos encontrava-se apenas abrigos *provisórios*, de emergência, logo abandonados pelo verdadeiro nomadismo dessas profissões.

Depois, verificou-se em outras áreas que havia uma certa *transmissão extradomiciliária*, tanto pelo *A. darlingi* como pelo *A.* (*K.*) *bellator*. E, finalmente, estudos mais recentes (10) deram certa evidência de que o *A. darlingi* estava desenvolvendo uma *resistência de comportamento*: alimentava-se no domicílio e fugia para abrigos extradomiciliários, escapando, assim, à acção do insecticida.

Até agora não há evidência de verdadeira resistência ao D. D. T. por parte dos transmissores da malária no Brasil. Entretanto, certos factos, como a necessidade de doses cada vez maiores de insecticida, observada em algumas regiões, *permitem suspeitar que o* A. darlingi *começa a desenvolver esse fenómeno*. Essa é a outra eventualidade em que o método do sal cloroquinado terá segura aplicação.

Resumidamente, vejamos, então, as amplas indicações que terá, possìvelmente, o novo método. De um modo geral, o sal cloroquinado tem a sua aplicação ditada por ocorrências de ordem *epidemiológica* e *económico-administrativa*:

Indicações do método do sal cloroquinado

- 1) Epidemiológicas
  - *A*) transmissão extradomiciliária.
  - *B*) resistência ao insecticida.
    - resistência pròpriamente dita.
    - resistência de comportamento.
- 2) Económico-administrativas
  - *C*) áreas extensas, com demografia reduzida e escassos meios de transporte.
  - *D*) áreas com habitações primitivas, desprovidas de paredes, não podendo ser protegidas.
  - *E*) agrupamentos humanos nómadas ou seminómadas com habitações de emergência.

Portanto, de um modo geral, *o método poderá ter larga aplicação na América, na Ásia e na África, em áreas malarígenas de condições bioclimáticas e demográficas semelhantes à Amazónia*. E, assim, também, em regiões onde os vectores desenvolveram resistência ao D. D. T. Como exemplo para o primeiro caso, citamos a península do Yucatan (México): florestas com abrigos de emergência dos trabalhadores nómadas da indústria extractiva, que não podem ser protegidos pela dedetização. Para o segundo caso, os exemplos são relativamente numerosos. No que diz respeito à África Tropical, é interessante conhecer a opinião de Pampana. Considerando as dificuldades enfrentadas pela dedetização, ele acha prematura a ideia da erradicação da malária nessa vasta região, e diz: «Si fuera posible aumentar el periodo de acción residual de los insecticidas rociados sobre paredes que los absorben rapidamente, tal vez el problema cambiaría, como asimismo si la distribución de cloroquina o pirimetamina mezclada en la sal de cocina pudiéramos hacerla llegar com éxito y sin contratiempos a las poblaciones africanas» (20).

Finalmente, *mesmo em áreas eficientemente dedetizadas, o novo método poderá servir para apressar a eliminação da «malária residual», que às vezes permanece por longos anos, devido a uma certa transmissão extradomiciliária.*

V — *Repercussão do novo método nos meios internacionais*

Os primeiros malariólogos estrangeiros a conhecer o novo método foram os Drs. C. A. Alvarado, chefe do C. O. M. E. P. da R. S. P. A., e A. Gabaldon, do «Quadro de Peritos de Malária» da O. M. S. Ambos, em 1952, manifestaram, verbalmente, a sua confiança no novo método. Nessa época, o Dr. Alvarado, em conferência (2), assim se expressou: ... «Estaría asi descubierto el procedimiento para dominar la malaria donde fallaran los maravillosos insecticidas de acción residual.»

Por sua vez, o Dr. Gabaldon, no V Congresso Internacional de Medicina Tropical e Malária (Istambul, Agosto-Setembro de 1953) (11), fez as seguintes considerações:

«I want to congratulate Dr. Pinotti for having introduced a method which, I believe, makes possible for the first time the application of drugs for malaria in civilian life.»

Na quinta sessão do Expert Committee on Malaria da O. M. S. (Istambul, Setembro de 1953) apresentámos outra comunicação sobre o método do sal cloroquinado. No seu relatório assim se manifestou o referido Comité (3, 11):

«Where a community is living under conditions which totally preclude the application of antimosquito measures, the use of antimalarial drugs may be the only practicable method of controlling the disease. An ingenious method of distribution by mingling the drug with table salt has been used...»

Na Conferência Inter-Regional para as Regiões Europeias e Leste do Mediterrâneo da O. M. S. (Atenas, Junho de 1954), o Dr. E. J. Pampana, chefe da Secção de Malária da O. M. S., informou que esta solicitara ao Dr. Robert Coatney a realização de investigações sobre o sal cloroquinado (12). O Dr. Robert Coatney confirmou integralmente o que anunciávamos, tendo associado também ao sal a pirimetamina, com bons resultados (15, 21).

«The results of the control studies show that each test drug suppressed sporozoite-induced Chesson strain *vivax* malaria during the entire life of the actual test and for 28 to 40 days after the test in the case of pyrimethamine and for 33 to 43 days after chloroquine.»

Na 6.ª Reunião do Expert Committee on Malaria da O. M. S. (Atenas, Junho de 1956), o sal cloroquinado figurou na agenda dos trabalhos. O comité, discutindo os aspectos relacionados com o emprego de drogas antimaláricas em campanhas de erradicação da doença, assim se manifestou:

«The Committee took note of Pinotti's method of mass administration of chloroquine mixed with table salt, which might be of value in some circumstances...»

Na 2.ª Reunião do Advisory Committee on Malaria da R. S. P. A. (Maracay, Venezuela, Dezembro de 1956), o Dr. Bustamante apresentou resultados do emprego do novo método, tendo o Dr. Fred L. Soper, director-geral da R. S. P. A., declarado que esse havia sido um dos mais importantes factos levados àquela reunião (13).

Na 1.ª Reunião de Chefes de Serviços Nacionais de Malária de Países Sul-Americanos (Cochabamba — Bolívia, 1957), o novo método também foi reconhecido como arma valiosa nos programas de erradicação da malária. Aprovou-se a seguinte resolução (14):

«Que se mantenha o nome de «Método Pinotti» para as misturas de sal de cozinha com cloroquina, daraprim ou outra qualquer droga antimalárica.»

Em vários países sul-americanos já se cogita do emprego do sal cloroquinado. O Dr. Gabaldon comunicou-nos que vai fazer uso do sal cloroquinado no sul da Venezuela, onde acredita que o D. D. T. tenha falhado na erradicação da doença, devido, provàvelmente, à transmissão extradomiciliária pelo *A. darlingi* (16).

O Dr. E. J. Pampana refere recentemente: «Já é tempo de utilizar o método no campo» («We now feel that the time come to utilize the method in the field») (17).

O Dr. M. G. Candau, director-geral da O. M. S. (19) assim se manifestou (Junho, 1957): «The work undertaken under W. H. O. sponsorship on administration of pyrimethamine or chloroquine in salt used in the daily diet has largely confirmed the results of Pinotti who originated this method using chloroquinized salt. The use of medicated salt for mass malaria prophylaxis may be a valuable method of control in certain special circumstances.»

Finalmente, o Dr. Pampana (20), em trabalho recente (1958), emite taxativamente a seguinte opinião: «La eradicación por medicamientos solo parece posible en algunas localidades elegidas a título experimental, o cuando, mezclados con la sal de cocina, tengamos la seguridad de poder hacerlos llegar a la totalidad de la población.»

Por conseginte, estão definitivamente aceitos nos meios internacionais especializados a eficácia e o valor do novo método de profilaxia da malária por nós introduzido. Tanto assim que, na campanha de erradicação ora iniciada no Brasil, com a cooperação das entidades internacionais de saúde, os trabalhos na Amazónia serão feitos com o sal cloroquinado.

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GENERAL DISCUSSION

Dr. Giulio Raffaele (Italy) — Je désire attirer l'attention du Congrès sur les résultats que nous avons eu en Italie en essayant la méthode de Busvine et Nash pour investiguer le degré de tolérance des anophèles italiens au DDT.

Nous avons trouvé que toutes les espèces du group *maculipennis,* y compris *A. sacharovi,* ont un degré de tolérance au DDT élevé, particulièrement quand les expériences sont exécutées dans les mois pendant lesquels la reproduction des anophèles est très active. Les anophèles jeunes montrent un haut degré de tolérance.

Quoique la tolérance des deux vecteurs, *A. labranchiae* et *A. sacharovi,* soit élevée, l'éradication du paludisme, qui a été atteinte en Italie depuis plusieurs années, n'a pas été d'aucune façon compromise par la tolérance observée.

Dr. G. Davidson (U. K.) — Recent advances in our work on insecticide resistance in anophelin mosquitoes in the Ross Institute are:

1 — DDT resistance in *A. stephensi* from Iraq: crossing this resistant strain with a susceptible strain of the same species from India have shown in some cases indications of a monofactorial mechanism operating but not always;

2 — The association between resistance and hybrid sterility in *A. gambiae* found, when some resistant and susceptible strains of this species were crossed, does not apparently occur when the susceptible and resistant strains are derived from one and the same population;

3 — Practical implications are now indicated by our laboratory studies. The use of descriminatory dosages for the detection of resistance is now preferred to a comparison of medium lethal concentrations.

Dr. Sabbar Farman Farmaian (Iran) — Tout en soulignant l'importance des matières exposées ce matin, je tiens à exprimer mon admiration aux orateurs, pour les travaux présentés, et aussi remercier

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Monsieur le Président de l'occasion qu'il me donne d'ajouter quelques mots.

Les docteurs Mattingly & Busvine ont séparément attiré l'attention sur les problèmes complexes de génétique en rapport avec le développement des phénomènes de la résistance aux insecticides chez les divers vecteurs. A mon avis ce point est d'une importance capitale. Aujourd'hui, pour les malariologistes et ceux associés en plusieurs années d'effort, pour contrôles le paludisme, la menace de l'ombre projetée et envahissante de la résistance aux insecticides par les vecteurs ne peut donner que de l'inquietude. Il sera peut être possible d'y parer et d'y remedier par la conjugaison des travaux de recherche, collaboration étroite des généticiens, malariologistes et tout ceux nombreux interessés par la question.

A propos du rapport du Dr. Daggey, sur la résistance au DDT des *A. stephensis,* en Arabie Saudite, que est un travail fort intéressant, je ne dois d'ajouter que cette résistance encercle aujourd'hui toute la région du Golf Persique. Nous sommes trouvés face, en effet, l'automne 1957, à une épidémie brusque de malaria en Abadan et le district avoisinant, qui ont dans l'ensemble une population de plus de 300 000 habitants. La ville de Abadan est un grand centre industriel, petrolier et aussi un port très animé du sud de l'Iran. Pendant une période de près de 5 ans, suivant le début de la campagne de lutte antipaludique en Iran, nous n'avions rencontré dans cette région que des cas de rechutes de moins en moins nombreux et aussi quelques cas de paludisme d'importation. L'épidémie brusquement apparue (cinq mille cas en l'espace de quelques semaines) fût aisément circonscrite et l'enquête révelait la résistance de *A. stephensi* au DDT dans cette région de l'Iran. Cette résistance, bâtie dans un interval de temps plus ou moins long, avait une manifestation récente. Peut être des chutes de pluies avancées et exceptionnelles de cet automne, en comparaison des années précédentes, ont pu contribuer comme causes favorisantes ou servir de facteur précipitant au développement et multiplication d'une race d'anophèles déjà à l'état de résistance latente.

Il va de soi que, depuis cette date, notre programme de pulvérisation dans cette région est basé sur l'emploi de dieldrine; de même que dans toute la zone sud de l'Iran où *A. stephensi* se trouve présent même associé à d'autres vecteurs.

De plus, pour prévenir toute surprise future, des tests systématiques de résistance aux insecticides utilisés sont effectués, grâce aux moyens mis à notre disposition par l'O. M. S., périodiquement et regulièrement dans les laboratoires regionaux des Services d'Eradication du Paludisme.

Dr. ALEXIS GRJEBINE (France) — Je voudrais attirer l'attention sur l'importance des études taxanomiques en épidémiologie, comme Mattingly l'a mis en évidence.

Il n'y a pas longtemps, à Madagascar on croyait avoir à faire à une population anophelienne purement africaine, mais depuis 6 ans nous avons procedé dans toute l'île à une recherche de toutes les espèces de moustiques pour l'établissement de la carte des anophèles. Après une prospection d'environ 1500 localités, le nombre des espèces a doublé. 10 espèces nouvelles pour le monde ont été trouvées par nous au cours de ces dernières années. Leur étude taxonomique et biologique a été indispensable pour comprendre ce que représente la population anophélienne de Madagascar. Certaines de ces espèces indigènes sont très nombreuses et jouent peut être un rôle épidémiologique important. Les espèces comme *A. mascarensis* de Meillon et *A. pauliani* Grjebine piquent les indigènes à l'intérieur et l'extérieur des habitations et ont été trouvées infectées par des microfilaires au stade infectif. Nous indiquons qu'avant de procéder à une enquête paludologique il est indispensable:

De s'assurer que toute la population anophélienne a été dépistée;

De faire d'abord la répartition detaillée des anophèles dans le territoire;

Et de décrire toutes les nouvelles espèces.

Dr. M. H. HOLSTEIN (France) — Je désire attirer l'attention du Congrès sur l'importance d'une collaboration étroite entre les Services d'Agriculture, qui prennent un grand développement dans les pays où la disparition des grandes endémies permet d'envisager de grands travaux agricoles, et les Services dont dépend le contrôle (ou l'éradication) du paludisme.

En effet, le jeune état du Ghana doit, l'an prochain, protéger le cacao contre les capsides par les pulvérisations, à l'échelle nationale, de H. C. H. Le risque que présente un tel projet, notamment le développement de la résistance chez les anophèles, ne doit pas être sous-estimé et une coopération indispensable doit s'établir entre services agricoles et médicaux de ce pays.

Dr. R. H. DAGGY (U. S. A.) — In Saudi Arabia, we are now having a new problem with dieldrin resistance in *Anopheles pulcherrimus*. Although this may represent a potential problem in *eradication* attempts, we do not feel it will greatly affect malaria control efforts at first for the present. These observations have been made recently by Dr. Robert L. Peffly, Arabian-American Oil Co. entomologist in the same oases where we have previously reported DDT resistance in *Anopheles stephensi*.

Dieldrin has been used since 1955 in oases of Eastern Saudi Arabia — and, although *A. stephensi* has now almost disappeared, *A. pulcherrimus* is now being found in increasing numbers in sprayed shelters. Laboratory tests made by Dr. Peffly using the W. H. O. technique have shown a considerable increase in M. L. C. in the adults now resting on dieldrin surfaces as compared with data collected two years ago. These data are being presented to the *Bulletin W. H. O.* for publication in more detail. Similar data are available for *A. coustani tenebrosus*, although this species apparently is not considered as even a potential vector at present.

Although we have no local evidence at present that *A. pulcherrimus* is a vector, reports in the literature indicate that it can transmit in some areas. If even low grade transmission by *A. pulcherrimus* occurs in spite of dieldrin applications, our local malaria eradication goal may be endangered. Both *A. pulcherrimus* and *A. coustani tenebrosus*, unlike *A. stephensi*, are still susceptible to DDT — hence a combination or alternation of the insecticides may solve any problem that may arise in this regard. We would be very appreciative if anyone can give us more recent data on *A. pulcherrimus* as a vector species. We hope to make a series of dissections — especially of specimens collected in houses of new cases or relapses as well as in the homes of children found parasite positive in our forthcoming November village surveys in order to collect more information on this subject.

3RD SESSION — *Friday, September 12th, 3:00 to 4:30 p.m. Room D*

The meeting was held under the Chairmanship of Dr. P. G. Sergiyev and Dr. G. A. Livadas.

The Rapporteur was Dr. O. Mastbaum and the Secretary was Dr. Jorge Melo Vieira.

The following papers were presented and discussed:

DEMOGRAPHIC EFFECTS OF MALARIA WITH SPECIAL REFERENCE TO THE STABLE MALARIA OF AFRICA

Dr. I. A. MacGregor

The effect that malaria exerts on any population is largely governed by its epidemiological pattern in that population. MacDonald (1957) has drawn attention to the two epidemiological extremes in which the disease exists, one where instability is the dominant feature and malaria is characterised by substantial seasonal swings in incidence or by cyclical epidemics, the other where stability is the key-note and a malaria remarkable for its uniformity ensues. Although the factors responsible for the shaping of the epidemiological pattern of any area are many and varied, their contributions can eventually be resolved and expressed as the development of immunity in the population at risk. In the development of this communal malarial immunity two factors are of basic importance: firstly, the frequency of infective inoculation and, secondly, the duration of exposure of the community to infection. Where populations have been exposed to frequent heavy inoculations for many years, a high degree of immunity is achieved and the epidemiological pattern that ensues is one of stability in which malaria pursues a relatively constant and predictable course year after year. On the other hand, where the population is exposed to infrequent inoculation or to intense infection for brief periods a high level of communal immunity is not achieved and an unstable pattern results.

It is in those parts of the world where it occurs in its unstable extreme that the importance of malaria is most clearly recognised. Here,

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the entire population regardless of age is vulnerable and inoculation tends to be followed by clinical illness. The effects of the disease are obvious not only upon the health statistics of the community but also upon its economy. The cyclical epidemics of the Pubjab as described by Christophers (1911) constitute a striking example of this type of malaria. These swept over thousands of square miles of territory, affected a population of millions, greatly inflated the morbidity and mortality rates in all age groups, and left a legacy of economic and administrative chaos.

If the demographic importance of unstable malaria is obvious the same cannot, unfortunately, be said of the disease existing in circumstances of high stability for then its ubiquity confuses accurate diagnosis. No longer can the incidence of parasitaemia be taken as an index of clinical illness and the apparently logical deduction that clinical illness in a parasitised patient is malarial in origin is frequently wrong. The health of the community is determined by many diverse factors operating against a background of parasitaemia, and the assessment of the contribution made by malaria calls for detailed and painstaking investigation. The complexity of the situation is reflected in the paucity of precise information available on the demographic importance of stable malaria. Malariometric data from an area of stable malaria tends to yield a constant picture where parasite rates and densities reach their peaks in young childhood and thereafter descend to reach low levels in adolescence and adult life. These data, although they indicate a malarial immunity increasing with age and that, in consequence, malaria is likely to exert its maximum effects on infants and children, give no precise information of its effects on different age groups. However, such a picture can be constructed by piecing together information from those parts of Africa where malaria pursues a stable course.

It has been established that in areas of intense transmission, the incidence of parasitaemia in infants under three months of age is commonly lower than can be explained by malariometric data (Garnham, 1949; Bruce Chwatt, 1952; Gilles, 1957) and four principal hypotheses have been propounded to explain this insusceptibility. These are:

1) The presence of effective passive immunity inherited from the mother (Blacklock and Gordon, 1925-*a*).

2) The inability of foetal haemoglobin to support plasmodial development (Allison, 1954-*a*).

3) The inability of plasmodia to develop when the host's diet is a milk one deficient in para-amino-benzoate (Maegraith *et al.*, 1952; Hawking, 1954).

4) Selective vector biting (Muirhead Thomson, 1951).

Although at the present moment our knowledge is insufficient to permit an accurate assessment of the value of these hypotheses an observation of Davies (1954) is of importance. He showed that whereas malaria was responsible for 7 % of admission to hospital of Ganda infants under three months of age, in non-Ganda infants of the same age group it was responsible for 65 % of admissions. Pointing out that, although both Ganda and non-Ganda tribes lived in the same hyper-endemic environment, the former were the natural inhabitants of the area and the latter were immigrants Davies concluded that the difference was probably attributable to the failure of non-Ganda mothers to hand on to their infants a passive immunity effective against the strains of *P. falciparum* prevalent in the area. Certainly it does not seem possible to explain the discrepancy solely by the hypotheses of selective vector biting or the protective value of foetal haemoglobin.

The period of relative insusceptibility terminates with the onset of the primary attack. In Tanganyika, Wilson (1936) observed that once infection occurred infants became pyrexial and ill. Garnham (1949) in Kenya found little deterioration in health beyond pyrexia. In Nigeria, Bruce Chwatt (1952) could demonstrate a markedly deleterious effect in only 15 % of primary attacks — an incidence identical with that reported by van Nitsen (1941) from the Belgian Congo. In the Gambia recent investigations (McGregor *et al.*, unpublished) have shown that with few exceptions the primary attack is exceptionally mild — in some instances being confined to a transient asymptomatic parasitaemia. Clearly then the full debilitating effects of malaria in infancy cannot reside in the primary attack. To elucidate this point the Gambia investigations were extended to observe the course of subsequent malaria attacks and it was found that as the age of the infant progressed so the importance of malaria increased. Subsequent infections gave rise to dense parasitaemia and to severe clinical illness and the disease was seen to exert its most profound effects in the second year of life. Earlier Gambian investigations (McGregor *et al.*, 1956-*a*) indicated that malaria caused the bulk of its damage before the thirtieth month of life. It retarded the normal pattern of growth, it produced considerable anaemia and it appeared to contribute materially to mortality rates. However, in the second half of the third year of life children appeared to gain ascendency over their infections and marked clinical improvement despite the persistence of moderately dense parasitaemia occurred. This marked decrease in clinical illness enabled children to regain lost ground rapidly and by the 36th month of life they compared favourably with children brought up in the same environment but protected from birth by weekly chemoprophylaxis. The clinical improvement in the malarious children was associated with a significant increase in the gamma globulin content of their sera.

The effect of malaria on young West African schoolchildren has been studied by Colbourne (1955) and by Archibald and Bruce Chwatt (1956). By suppressing the disease for twelve months in seven-year old children, the former found little material benefit followed the protection. In suppressing the disease from the 6th to the 8th year of life the latter observed a significant gain in weight when the protected group was contrasted with an untreated control but could demonstrate no other definite health improvement. In both these investigations members of the control groups appeared to possess effective antimalarial immunity.

The behaviour of malaria in a small group of Nigerian adults has been investigated by Bruce Chwatt (1957) who showed that, although parasitaemia could be demonstrated in only 25 % of subjects at a single examination, serial observations showed that 90 % harboured parasites in the blood at some time over a 9-month period. The parasitaemia tended to be of low density but in several cases subclinical peaks developed. Exposure to stress produced no obvious effects on parasite density. Finally the inoculation of heavily parasitised blood obtained from schoolchildren was inoculated into 16 adults, 9 of whom later developed heavy parasitaemia. In all cases the increase in parasite density was either asymptomatic or associated with only mild clinical effects.

From this composite picture of stable malaria in Africa a pattern of host-parasite relationship emerges. The individual passes through five successive stages each of which appears to be shaped by the immunity of the host. Stage one represents the period of relative insusceptibility where inherited immunity appears to reinforce some transient malariostatic phenomenon, e. g. foetal haemoglobin, to give freedom from parasitaemia. Stage two represents the primary attack in which inherited immunity mitigates the clinical effects but does not suppress parasitaemia. Stage three coincides with the trough of host immunity — inherited antibodies have been exhausted and actively acquired ones have not yet been produced in effective quantity. Stage four represents the acquisition of the first phase of active immunity, the antitoxic immunity of Ziemann (1924), and is characterised by a rapid decline in the severity and frequency of clinical illness despite the persistence of relatively dense parasitaemia. The fifth and final stage is reached when antiparasitic immunity is achieved and parasitaemia drops to a very low level. The age at which stage five appears is probably governed mainly by the frequency of infection and the number of antigenically dissimilar strains of plasmodia present in the area.

What could be termed an additional stage of immunity has been postulated by Bruce Chwatt (1956). Reporting hyperplasia of the foetal spleen in Africans he suggests that this could be brought about through stimulation by some substance entering the circulation via the placenta. The substance may be a specific maternal antibody or it may be an antigenic product of the malaria parasite and by activating the foetal lymphoid macrophage system in utero it may forearm the infant for its first malaria infection.

The high degree of immunity gained by the community in areas of stable malaria is purchased at considerable cost in terms of morbidity and mortality in infants and young children. In Southern Nigeria the disease has been shown to be directly responsible for 9 % of deaths in infancy and for 14 % of deaths in children between 1 and 4 years of age, Bruce Chwatt (1952). In the Belgian Congo, Duren (1951) estimates the mortality rate from malaria to be between 24.5-40 per thousand in infants, 9.4-15.2 per thousand between the first and second years of life and 6.4-10.5 per thousand between the third and fourth years of life. It has been estimated that approximately 12 % of all deaths in African children between birth and four years of age are due directly to malaria (Report Second African Malaria Conference Lagos, 1955).

These rates are impressive particularly when it is remembered that they do not take account of the importance of malaria as a contributory cause of death. Infancy and young childhood are particularly testing periods for the growing individual. Drastic changes in feeding habits and in diet take place, and respiratory infection, alimentary upsets and the numerous infectious diseases of childhood abound at this time. It is difficult to imagine that against this background malaria with its severe clinical illness and its attendant anaemia does not frequently contribute indirectly to mortality. Some indication of the importance of this contribution can be gained by contrasting figures of crude mortality in hyperendemic areas before and after the introduction of antimalarial measures. Janssens (1952) reports a reduction in infant mortality rates from 308 per thousand to 132 per thousand following mass weekly chemoprophylaxis in a hyperendemic area of the Belgian Congo and he infers that although improvement in existing medical services contributed to this reduction the elimination of malaria was probably the principal responsible factor.

With the acquisition of immunity the obvious effects of malaria upon the vital statistics of the community diminish until a state approaching commensalism is achieved in adult life. Little is known, however, of the cost to health and physical capacity of maintaining this admirable host-parasite equilibrium. Although attention has frequently been drawn to the possible deviation of protein and other essential nutrients to meet the requirements of plasmodial development and of the host's immunological defences to date little convincing evidence has been adduced to demonstrate important and significant improvements in the nutritional state of adults following malaria eradication from hyperendemic regions. The benefits that accrued to adults from six years of malaria control — not eradication — in a rural village in a hyperendemic area of the Gambia were confined to females and limited to significant improvement in mean haemoglobin values and in the incidence of mucosal lesions attributed to deficiency of vitamins of the «B» complex (McGregor, 1956-*b*). Certainly much more investigation of this aspect of stable malaria is indicated.

Equally obscure are the effects of stable malaria upon the expectant mother. Bruce Chwatt (1952) has demonstrated a raised parasite rate in Nigerian parturient women which suggests that the physiological stress of pregnancy produces some attenuation of anti-parasitic immunity. McGregor and Smith (1952) found higher parasite rates in primipara than in multipara in the pregnant women of a rural Gambian village. In Sierra Leone, Blacklock and Gordon (1925-*b*) found no evidence that parasitaemia predisposed to abortion but demonstrated that still-birth and neonatal mortality rates were higher in babies born with an infected placenta. In Kenya, Garnham (1938) was unable to confirm this latter observation. In Nigeria, Bruce Chwatt (1952) found the birth weights of infants born with infected placentae to be significantly lower than those with uninfected placentae but could not demonstrate any relationship between neonatal mortality and placental infection. His observations have since been confirmed in Western Nigeria by Archibald (1956) and by Cannon (1958). The latter demonstrated the mean birth weight of 130 infants with infected placentae to be significantly (312 grammes) lower than that of 262 infants born with uninfected placentae. Adopting a birth weight of less than 2,500 grammes as the criterion of prematurity he showed the incidence of prematurity to be significantly higher when plasmodial infection of the placenta existed. Cannon also noted an apparent negative correlation between parity of the mother and placental infection and suggested that this might be due to the gradual acquisition of higher degrees of malarial immunity. Clearly the effects of stable malaria on the expectant mother and her developing foetus offer a fruitful field for further investigation.

Before leaving the subject of the morbidity and mortality of malaria, mention must be made of the effect that the presence of abnormal haemoglobins might have on the pattern of malaria in a community. Allison (1954-*a*) and Raper (1955) have shown that individuals with sickle haemoglobin in their erythrocytes possess some natural resistance towards *P. falciparum* infections and in consequence develop a less dense parasitaemia than do individuals whose red blood cells contain only adult haemoglobin. Raper (1956) has advanced evidence to suggest that children who are heterozygous for the sickling gene have a greater chance of survival than normal children when both are exposed to malaria infection. The importance of these observations is obvious when the high incidence of the sickle cell trait in certain populations is considered. Allison (1954-*b*) has demonstrated an incidence of 30-40 % in some African tribes.

Haemoglobin «S» is but one of many abnormal haemoglobins that have been described and the effect that many others exert on the developing plasmodium remains to be investigated. It is too early, as yet, to estimate how much the presence of these abnormal haemoglobins may affect the malaria morbidity and mortality in different communities but current evidence suggests their role might prove an important one.

The study of the demographic effects of malaria enables one to predict with some accuracy the results that campaigns of control or eradication might be expected to yield. In areas of unstable malaria control or eradication is likely to be followed by considerable improvement in the health of all age groups of the population. This, by enhancing productivity, may in turn so improve the economy of the area that at least part of the cost of the antimalarial measures may be recovered. A decrease in death rates of children and adults will become obvious and the rates of abortion, still-birth and neonatal mortality will be reduced. In areas of stable malaria the benefits of eradication will be most apparent in the young age groups. The incidence of prematurity may decline, neonatal mortality may be reduced, infant mortality and death rates in young children will be reduced and the health of infants and children will be substantially improved. From such information as is available the health and physical fitness of the adult population, with the possible exception of pregnant women, are not likely to improve materially and consequently no marked economic advance can be expected. The effects of malaria control as opposed to malaria eradication may logically be expected to vary according to the level to which transmission is reduced. Highly successful control will produce effects similar to eradication but poor control may, by decreasing the frequency of infective inoculation and consequently communal immunity, bring about a state where adults as well as children suffer from the ravages of the disease.

It would appear therefore that wherever malaria exists as an important disease eradication or successful control measures will eventually produce a substantial increase in population — a state of affairs which will undoubtedly be attended by specific and urgent problems.

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MALARIA CONTROL PILOT PROJECT IN WESTERN SOKOTO, NORTHERN NIGERIA
A REPORT ON FOUR YEARS' RESULTS

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1. *Introduction*

There is at present a campaign under way in North-West Nigeria for the control of malaria in a population of half a million people. That campaign developed from a pilot project commenced in April 1954 as a joint endeavour planned and directed by the Federal Malaria Service of Nigeria, executed by the Medical Department of the Northern Region of that country, substantially assisted by the United Nations Children's Fund and sponsored and helped by the World Health Organization[2]. It is with that pilot project that the present paper deals.

The project covered 600 sq. miles of Gwandu Emirate in Sokoto Province in the extreme north-west of Nigeria, a rural area inhabited

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[2] A more detailed report covering all phases of this project and including some hitherto unpublished material is being prepared for publication at a later date.

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by about 130,000 people dwelling mainly in characteristic round mud huts covered with thatch. Ecologically the area belongs to the Sudan Savannah type of country, with an average annual rainfall of 32 inches (820 mm) of which 31 inches (800 mm) fall between May and October. The dry season is relatively cool during October-December and hot from February to early May.

The occurrence of holoendemic (stable) malaria in an area with such a marked seasonal rainfall is due to the fact that the breeding activity of the two main vectors *A. gambiae* and *A. funestus* shows an overlap throughout the year and thus extends the transmission period to over 9 months (table 1).

TABLE 1 — *Seasonal variations of vector densities. Numbers per room day of female* A. gambiae *and* A. funestus *in Western Sokoto (Pre-control period)*

		Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sep.	Oct.	Nov.	Dec.
Rainfall	ins.	0.01	0.03	0.17	0.52	2.65	4.39	7.07	10.65	6.04	0.73	0.04	0.0
(mean)	mm.	0.3	0.9	4.3	13.2	67.5	112.0	179.0	271.5	153.0	18.6	1.2	0.0
A. gambiae	Dogandaji	0.3	0.5	0.3	1.5	0.5	1.2	9.2	55.0	121.0	31.0	3.0	20.5
	Argungu	8.3	28.5	16.0	15.8	23.5	84.3	166.5	132.0	136.9	214.9	37.9	18.8
A. funestus	Dogandaji	2.8	1.0	1.8	0.0	0.0	0.0	1.2	7.8	13.5	31.5	10.5	3.0
	Argungu	5.0	3.8	5.4	1.0	0.3	0.0	3.7	4.3	10.1	51.7	39.5	12.6

Note — Dogandaji is a north-western Nigerian town in an area relatively free from surface water. Argungu is a north-western Nigerian town situated on the banks of the Sokoto river.

Malaria in the area of the Western Sokoto Pilot Project was holoendemic (stable), as is indicated in table 2 which shows spleen and parasite rates determined in pre-control surveys during 1953. As usual in Tropical Africa, the bulk of the infections were due to *P. falciparum,* but in the young age groups *P. malariae* averaged a specific rate of 15 %, while *P. ovale,* very variable in its frequency, did not exceed 0.5 % in large samples of the examined population.

The investigation of adult bionomics of the two main vectors revealed that *A. gambiae* is predominantly endophilic, although a small proportion of the population of this species could be found sheltering out of doors, usually in the vicinity of human communities. The same indoor characteristic applied to the biting activity of *A. gambiae*. On the other hand it was found, by the use of precipitin tests, that man was not the preferred host of *A. gambiae* and that this mosquito fed almost equally easily on domestic animals and particularly on horses. The habits

TABLE 2 — *Spleen and parasite rates in inhabitants of western Sokoto as observed at pre-control surveys during 1953*

Season	Age group	Spleen rate		Average enlarged spleen	Parasite rate	
		%	N	A. E. S.	%	N
March-April (period of minimum transmission)	Infants	32.0	50	1.5	40.0	50
	1 and 2	61.5	122	2.0	87.0	139
	3 and 4	83.5	120	2.2	91.0	132
	5, 6 and 7	63.2	147	1.8	71.0	145
	8, 9 and 10	55.4	167	1.8	53.9	128
	11 to 15 inclusive	38.8	255	1.8	36.4	216
	Over 15	8.8	80	1.8	17.5	80
September-October (period of maximum transmission)	Infants	45.5	22	2.5	79.5	34
	1 and 2	84.0	75	2.7	97.5	125
	3 and 4	93.0	142	2.7	98.8	175
	5, 6 and 7	86.2	339	2.3	92.5	358
	8, 9 and 10	65.3	351	2.0	81.0	365
	11 to 15 inclusive	51.5	235	2.0	60.9	268
	Over 15	11.1	9	1.0	33.0	139

of the second main vector, *A. funestus,* showed that it was rather more endophilic than *A. gambiae* and that its preference for human blood was greater, but by no means obligatory.

Other common local species such as *A. rufipes, A. coustani, A. pharoensis, A. nili, A. squamosus, A. flavicosta,* etc., play an insignificant part in the transmission of local malaria, in comparison with the two main vectors.

There was a difference between the infectivity of mosquitos caught in the dry season as compared with the rainy season. During a dry season survey when over 2 000 mosquitos were dissected only two (one *A. gambiae* and one *A. funestus*) were found to harbour sporozoites. A wet-season survey found in 1 500 dissections, a sporozoite rate in *A. gambiae* of 3.7 % and in *A. funestus* of 2.3 %. In terms of infective densities, these findings are arresting as shown in table 3.

Table 3 — *Average infective densities of two main vector species in W. Sokoto at seasons of maximum and minimum malaria transmission*

		Argungu	Dogandaji
Maximum transmission (October)	Average Anopheles density	266.6	62.5
	Sporozoite rate	3 %	3 %
	Average infective density	7.4	1.9
Minimum transmission (April)	Average Anopheles density	16.8	1.5
	Sporozoite rate	0.1	0.1
	Average infective density	0.02	0.002

2. *Initiation of the malaria control project*

The Pilot Project was intended to assess the comparative value of the three insecticides, D. D. T., B. H. C. and dieldrin, in effecting the control of malaria in a rural area of Northern Nigeria. The method employed was to divide the total project area into three zones each of which was treated with one of the insecticides. Spraying was carried out in continuous cycles of six months duration in such a way that dwellings were resprayed twice annually at half-yearly intervals. D. D. T. was applied at a dosage of 2 g of the p. p. isomer par m^2 (2.7 technical D. D. T. per sq. m), B. H. C. at 0.25 g gamma isomer per m^2 and dieldrin at first at 0.25 g per m^2. Wettable powders of various concentrations were almost the sole preparations applied and Hudson X-pert type compression sprayers were used. Spraymen were employed in squads of three under a literate recorder; eight of these squads covered the whole project area in six months, using Landrovers for long distance communications.

Assessment of the progress of the scheme made use of malariometrical, entomological and chemical methods. While these were all employed throughout the duration of the project, the pronounced influence of seasonal changes on the prevalence of mosquitos made it difficult to assess the effect of the control measures during the dry seasons. It was toward the close of each wet season that the best indications were obtained of the progress of control.

3. *The early results of the control measures: 1954 and 1955*

Spraying started in April, 1954, and at the close of that year bi-monthly collections from over 60 Capture Stations showed that reduction of vector densities of over 90 %, as compared with adjacent unsprayed areas, and of over 95 %, as compared with the previous state in the controlled area, had been achieved. There was some indication that the life-span of vectors in the sprayed areas was reduced, but there was little change in the malariometrical picture. There was little evidence at that time to show that one insecticide was more promising than another.

At the start of the third spraying cycle in April, 1955, the dieldrin zone was divided into two parts and one of them was sprayed with a higher dosage, of 0.5 g per m_2. At that time there was some optimism that it might prove possible to achieve control by means of only one application of insecticide annually if a toxicant of good persistence were applied at a heavy enough dosage.

Throughout the first half of 1955 there was continued evidence that although transmission was not eliminated its degree was greatly reduced in the area of the project. This gratifying trend was, however, reversed during the latter half of the year when the degree of transmission returned to its earlier level. This reversal was particularly marked in the dieldrin zone, and the possibility that it was due to the appearance of mosquitos resistant to that insecticide was investigated. Malariometrical findings closely paralleled the entomological; until the middle of the year, there was evidence of a substantial reduction of transmission, but this was followed by an abrupt increase toward the end of the year, especially marked in the dieldrin zone. Throughout 1955, the D. D. T. zone showed evidence of lowest transmission.

4. *The investigation of resistance*

In September, 1955, a new uncontaminated insectary was built in W. Sokoto and a fair supply of viable adult *A. gambiae* bred from pupae and larvae collected in the area became available for testing of susceptibility by the Busvine and Nash method (W. H. O., 1954). It was established by Elliott and Ramakrishna (1956) that adult *A. gambiae* from the dieldrin zone were eight times more resistant to dieldrin than the susceptible strain of this species. These results were presented at the World Health Organization's Conference in Lagos in December, 1955, where they were greeted with some scepticism.

In March, 1956, eggs from *A. gambiae,* collected at Ambursa, a village in the dieldrin zone, were sent to London by air and a flourishing colony of this strain was raised by the staff of the Ross Institute of Tropical Medicine. Investigation of that colony confirmed that the Ambursa strain of *A. gambiae* had a very high resistance to dieldrin and also a cross resistance to B. H. C. but no appreciable degree of resistance to D. D. T. (Davidson, 1956-*a*). Further investigation of that colony uncovered the genetic mechanism of the inheritance of this resistance (Davidson, 1956-*b*), which was shown to be monofactorial with incomplete dominance, the resistance to B. H. C. being invariably linked with the presence of dieldrin resistance.

It was possible to select two discriminating dosages of both dieldrin and B. H. C., the lower of which killed all susceptibles but not hybrids or resistants, the higher killing only resistants. For an exposure of one hour these dosages were 0.33 % and 4.00 % dieldrin and 0.025 % and

0.1 % gamma B. H. C. (Davidson, 1956-*b*) The discovery of this simple method of separating a mosquito population into its resistant components was applied from July to October 1956 in the field in W. Sokoto with a view to determining the extent and degree of resistance in the project area and to investigating its possible spread into surrounding areas (Armstrong *et al.*, 1956). This investigation confirmed the very high degree of dieldrin resistance not only in the dieldrin zone or the Pilot Project but in a contiguous area sprayed with B. H. C. It also revealed the presence of a small proportion of heterozygous resistant *A. gambiae* in neighbouring areas where no insecticide had been sprayed at all. It seems that some wild populations of *A. gambiae* in Northern Nigeria harbour a natural dieldrin/B. H. C. resistance gene in a very small number of individuals. Under the selection pressure of a residual spraying with dieldrin or B. H. C., the resistant fraction of the population increases rapidly with subsequent deterioration of control and increase of malaria transmission.

5. *Chemical investigations of insecticides*

Deterioration of insecticides in storage and sorption of deposits on mud surfaces was a well-known phenomenon. The insecticides used in the Pilot Project were subjected to continuous scrutiny to ensure that they were up to standard when used and that they were applied in the dosage intended. Their activity on sprayed surfaces was investigated and the chemical determination of their persistence was correlated with a bio-assay method. By the end of 1956, the techniques required to pursue these investigations had been mastered (Langbridge, 1955-*a*; Elliott, 1955) and it was known that in the first two weeks after spraying 40-60 % of all three insecticides was lost from the surface sprayed with them. After one month D. D. T. showed only a gradual rate of decline, and subsequent deposits cumulating at six-month intervals seemed to enhance its persistence. Dieldrin followed this pattern to some extent but the loss of B. H. C. from a sprayed surface continued at a high rate after the first two weeks so that 90 % was lost by the end of five weeks and no saturation by the superimposition of successive deposits occurred (Langbridge, 1955-*b*).

6. *Changes made following the appearance of resistance*

The discovery of the presence in the area of the Pilot Project of anopheles resistant to dieldrin led to the decision to discontinue the use of that insecticide. At the time of the appearance of dieldrin resistance in *A. gambiae* the presence of cross-resistance to B. H. C. was undiscovered, and in April 1956 it seemed that B. H. C. was giving good entomological control in the zone where it was applied. B. H. C. was therefore chosen to replace dieldrin but its dosage was to be 0.4 gms of gamma isomer per m^2 in an attempt to secure longer persistence. After the discovery of cross-resistance between dieldrin and B. H. C. the delay between planning and the procurement of supplies precluded the immediate changing of that decision.

B. H. C. continued to be applied in the original respective zone, but the frequency of cycles of application was increased from two to three (the dosage remaining at 0.25 gms gamma isomer per m^2) and an effort was made to cover this zone at least once during the period of maximum transmission. D. D. T. was sprayed as hitherto in its original zone.

The start of the fifth semi-annual cycle (April, 1956) saw the inception of this new programme, which continued through the sixth cycle and of course added a seventh cycle to the original B. H. C. (0.25 gms per m^2) spraying schedule.

The result of these changes was not conspicuous in 1956. In that year the D. D. T. zone achieved good entomological control except for the period from June to August; the original B. H. C. zone kept mosquitos at low densities but the zone where dieldrin had been used showed hardly any control. This was reflected in the malariometrical observations. Infant parasite rates were significantly lower in the D. D. T. zone but the overall changes in the project area were insignificant.

7. *Absorption of Pilot Project into a larger control campaign and results during 1957 and 1958*

April, 1956, was the date when it had been determined to apply the lessons learned in the Pilot Project to a more extensive scheme of malaria control. It had been hoped that this extension would take the form of a straightforward public health campaign but with so many unanswered questions this was obviously impossible. The larger campaign itself became something of an extended Pilot Project with continued scientific cover, and intense observation. In 1956, it extended the insecticidal cover to about 250 000 people and during 1957 to about 500 000. It used B. H. C. at a dosage of 0.4 gms gamma isomer per m^2 for the cycles which commenced in April and in September, 1956.

By April, 1957, the original Pilot Project programme was completed. It was obviously essential to attempt to deal with the highly resistant population of *A. gambiae* which was now dominating the original dieldrin zone and to that end this zone and a band of five miles round it were sprayed with D. D. T. The original D. D. T. zone was sprayed as usual with that insecticide, but (with the exception of the town of Kalgo which was still treated with dieldrin as an experiment) the rest of the control area was treated as part of the expanded scheme and received 0.4 gms gamma B. H. C. per m^2.

Not until September, 1957, were supplies of D. D. T. procured which enabled that insecticide to replace all others throughout the area of the extended campaign.

The result of the use of D. D. T. was gratifying. The first cycle nearly eliminated the vectors from most of the old dieldrin zone and marked indications of reduction in transmission were reflected in malariometric indices in the original D. D. T. zone. The reduction in the spleen rate was especially pronounced, but a substantial reduction of the parasite rates in infants and in young children was also observable in that area.

Table 4 shows the Anopheles Room Densities of *A. gambiae* and *A. funestus* combined and averaged for quarterly periods. The pronounced improvement effected by conversion to D. D. T. in both dieldrin and B. H. C. zones is obvious, as is the considerable measure of success achieved by D. D. T. in controlling these vector mosquitos since October 1956 in the D. D. T. zone.

Tables 5 and 6 show the change of the Spleen Rates in young children in the Pilot Project area during the period 1955-1958. This index of the endemicity of malaria decreased most markedly in the 1-2 age group and much less in the 3-4 age group. There was little change of the Spleen Rate in the older children. On the other hand the Spleen Rate in infants (not tabulated because of the fluctuation of this index depending on the age composition of the group) showed a specta-

TABLE 4 — *Average daily anopheles room densities — Females of* A. gambiae *and* A. funestus *combined — Recorded by quarterly periods*

Year	Quarter	Unsprayed areas	DDT zone		BHC zone		Dieldrin zone	
1953	Jan.	—						
	April	19.8						
	July	144.7						
	October ..	—						
1954	Jan.	31.6						
	April	34.1	4.2	Spraying commenced on April 1st, 1954				
	July	111.4	24.1		9.3	Spraying commenced in August 1954	26.2	Spraying commenced in July 1954
	October ..	80.9	4.3		2.9		6.8	
1955	Jan.	11.3	0.3		0.5		2.4	
	April	30.0	0.2		0.1		2.5	
	July	145.0	10.7		2.3		19.1	
	October ..	53.8	1.9		4.8		22.6	
1956	Jan.	7.4	0.3		1.3		8.8	
	April	11.2	1.2		1.4		6.4	Converted to B. H. C. in April 1956
	July	168.6	4.3		3.5		93.5	
	October ..	81.8	0.03		0.7		9.5	
1957	Jan.	15.1	0.03		0.1		4.8	
	April	12.1	0.03		0.3		7.1	Converted to D.D.T. in April 1957
	July	80.3	0.03		2.2	Converted to D.D.T. in Aug. 1957	3.7	
	October ..	93.9	0.0		0.3		0.1	
1958	Jan.	31.6	0.01		0.7		0,03	
	April	36.1	0.0		0.0		0.0	

TABLE 5 — *Spleen rates in children 1-2 years of age — Consolidated annual records for the pilot project and for the surrounding untreated areas*

Year	Unsprayed areas		Pilot project						Remarks
			DDT zone		BHC zone		Dieldrin zone		
	S.R.	N	S.R.	N	S.R.	N	S.R.	N	
1953-54	83.5	401	—						Figures shown under the column *Unsprayed areas* comprise data collected within the Pilot Project before spraying
1955	82.7	320	63.5	225	70.0	127	75.0	353	
1956	93.3	627	50.0	590	67.7	426	72.4	395	
1957	82.3	243	27.8	463	38.8	266	25.2	282	All zones converted to D. D. T. during 1957
1958 .... (incomplete)	—	—	0.6	189	—	—	—	—	

TABLE 6 — *Spleen rates in children 3-4 years of age — Consolidated annual records for the Pilot Project and for the surrounding untreated areas*

Year	Unsprayed areas		Pilot project						Remarks
			DDT zone		BHC zone		Dieldrin zone		
	S.R.	N	S.R.	N	S.R.	N	S.R.	N	
1953-54	92.4	458	—	—	—	—	—	—	Figures shown column *Unsprayed areas* comprise data collected within the Pilot Project before spraying
1955	92.0	134	83.8	93	79.0	90	86.4	139	
1956	87.3	355	78.3	120	69.0	207	79.6	126	
1957	89.0	198	35.3	272	39.3	247	27.8	216	All zones converted to D. D. T. during 1957
1958 .... (incomplete)	—	—	5.7	177	—	—	—	—	

cular decrease in the area of the Pilot Project and especially in the D. D. T. zone. It was zero in 1958 while it averaged 25 % during the previous 2 years. In the unsprayed area the Spleen Rate in infants averaged 55 %.

Tables 7, 8 and 9 show the annual Parasite Rates of infants and small children in the Pilot Project and in the untreated areas. The decrease in the D. D. T. zone of the Pilot Project is most marked though the speed of it is less than with regard to the respective Spleen Rate.

TABLE 7 — *Infant Parasite Rates — Consolidated annual records for the pilot project and for the surrounding untreated areas*

Year	Unsprayed areas		Pilot project					
			DDT zone		BHC zone		Dieldrin zone	
	P.R.	N	P.R.	N	P.R.	N	P.R.	N
1953-54	65.4	263	—	—	—	—	—	—
1955	56.2	428	34.0	162	57.5	113	44.1	392
1956	75.8	386	36.8	385	59.5	242	54.7	530
1957	79.5	137	21.6	348	32.0	150	33.4	324
1958 .... (incomplete)	85.8	85	7.9	76	—	—	—	—

Note — Remarks appearing in tables 5 and 6 refer also to tables 7, 8 and 9.

TABLE 8 — *Parasite Rates in children 1-2 years of age — Consolidated annual records for the Pilot Project and for the surrounding untreated areas*

Year	Unsprayed areas		Pilot project						Remarks
			DDT zone		BHC zone		Dieldrin zone		
	P.R.	N	P.R.	N	P.R.	N	P.R.	N	
1953-54	94.3	618	—	—	—	—	—	—	Pre-control survey covering some areas of the Pilot Project
1955	83.8	340	82.4	244	84.3	163	85.0	404	
1956	93.2	659	69.4	528	88.5	466	76.9	453	
1957	97.2	319	53.4	598	64.0	300	61.0	362	
1958 .... (incomplete)	—	—	34.5	197	—	—	—	—	

TABLE 9 — *Parasite rates in children 3-4 years of age — Consolidated annual reports for the pilot project and for the surrounding untreated areas*

Year	Unsprayed areas		Pilot project						Remarks
			DDT zone		BHC zone		Dieldrin zone		
	P.R.	N	P.R.	N	P.R.	N	P.R.	N	
1953-54	96.4	540	—	—	—	—	—	—	Pre-control survey covering some areas of the Pilot Project
1955	85.5	158	96.7	91	92.8	84	93.3	149	
1956	95.0	365	84.2	125	87.4	219	88.2	138	
1957	99.5	257	65.2	297	71.8	253	81.5	267	
1958 .... (incomplete)	—	—	48.3	182	—	—	—	—	

The differential effect of the decreased of transmission in relation to the age-group is obvious in these tables.

An investigation of the mean parasite densities in the respective age groups showed that the reduction of the transmission was also followed by a lower level of parasitaemia. This, added to the lower parasite rate now existing in the controlled area, represents a considerable reduction in the parasite reservoir in the protected population.

The effect of the adoption of D. D. T. over the whole area of the expanded scheme will not be clearly evident until late in the 1958 wet season. However, the results to date are encouraging. It is difficult to find either *A. gambiae* or *A. funestus* in the area whereas they remain as common as ever round about it, and now there are occasional villages in the centre of the controlled area where infants are entirely free of infection.

8. *The cost of the Project*

The fundamental principles governing the cost of this project extending over 600 sq. miles are the relatively low density of population with its repercussion on transport costs and the surface area to be sprayed per person on which in turn depends the amount of insecticide required. We have determined that the mean sprayable surface per inhabitant in Western Sokoto is approximately 29 sq. meters for the purpose of calculating our requirements. The 130,000 inhabitants live at an average density of 1.5 persons per hut; our spraymen can deal efficiently with about 45 huts per man per day.

With these fundamentals, the cost of the project has worked out at 3/- (41.7 U. S. A. cents) per person protected per annum when two cycles of spraying per year were carried out. 25 % of this was the cost of insecticide and 10 % the cost of labour; the remaining 65 % was made up of salaries of supervisory staff (25 %), transport costs (20 %), allowances for travelling, etc. (10 %), and cost of housing, spraying equipment, etc. (10 %).

SUMMARY

This paper describes the development of Western Sokoto Project in Northern Nigeria for the control of malaria and shows the results achieved in terms of vector room densities, spleen rates and parasite rates in infants and young children.

The effect on the Project of the discovery of the development in the controlled area of a population of *A. gambiae* resistant to dieldrin and to B. H. C. is detailed.

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TRENDS IN DEVELOPMENT OF RESIDUAL INSECTICIDES SPRAYING EQUIPMENT [1]

Synopsis

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Progress toward early eradication of malaria poses need for equipment of maximum efficiency with which to apply residual insecticides. Since the compression sprayer is the implement most commonly used in this work, every possible simplification and improvement within cost limits should be incorporated in it.

Certain such improvements already made or under consideration are discussed and evaluated. The need to impress manufacturers relative to equipment modernization is noted. Reasonable relaxation of characteristic specifications in order to permit incorporation of new or improved elements is suggested. Better daily cleaning and maintenance supervision is stressed.

Malaria as man has known it for thousands of years, may soon yield to complete eradication. Something which seemed a fantastic dream only twenty years ago will soon become a reality.

Belief that eradication is attainable has prompted reappraisal of fundamental factors involved in assuring this end. Primarily, success should be attained while low cost insecticides are still effective against the transmitting host.

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Knipe, F. W. — *Residual insecticides spraying equipment*

It has been said by Professor D. E. H. Frear, of the Pennsylvania State University that, «two factors affect the efficiency and cost of insect control by contact with residual sprays. These are distribution and persistance. To be most effective in insect control the spray deposit must be distributed on the treated surface in such a way as to provide maximum contact; and once deposited, the longer the deposit persists the more economical the control becomes».

Thousands of sprayers must be used to apply millions of pounds of this insecticide in the most effective manner. To apply either too much or too little is wasteful. To apply the correct quantity requires the best equipment procurable.

In the opinion of the author, modifications recently made to malaria control equipment have outpaced those made to similar types of sprayers used for other pest inhibition purposes. In fact, the identifying tool of the malaria control fraternity is the comparatively simple, highly versatile and rather inexpensive hand compression sprayer. It is the best tool thus far developed with which to apply residual sprays to surfaces where anopheles mosquitoes habitually rest. Its present superior design is the result of numerous suggestions for improvement made by many persons attending this Congress. Often these improvements have been incorporated only after repeated requests to fabricators who are often reluctant to incorporate new ideas in existing models.

Certain rather rigid specifications have been established for this tool. These should be made sufficiently flexible to permit inclusion of proven modifications instead of holding the end product to hard and fast rules.

The general trend toward improvement in compression sprayers has been quite logical.

Firstly, the apparatus should be designed to assure operational efficiency without unduly tiring the operator. This is an extremely important point where large labor forces are employed.

Secondly, the design must be such that unskilled labor may be taught how to make minor field adjustments.

Within recent years the author has re-orientated his thinking relative to the interpretation of the attitude of the workman toward the sprayer. Heretofore design techniques were established to make the equipment «fool proof». To a degree this may be good practice, but even an inefficient operator is curious to know how his tool functions. He cannot

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 362-367, 1959

be completely stopped from tampering with it. Therefore sprayer elements which must periodically undergo inspection or adjustment should be designed to permit the unskilled operator to inspect them and to understand how they function. He will usually follow clearl, given instructions, particularly if it is apparent to him that proper adjustment means less tiring labor.

The design must be streamline assembled to permit rapid and adequate cleaning. Approximately 95 percent of good quality sprayer failure comes about through inadequate daily cleaning. This in turn, is due to faulty maintenance supervision. It requires from three to five minutes to completely flush out a sprayer; minutes exceedingly well spent when one considers the time lost and material wasted when such a daily program is not enforced.

Residual insecticides must be uniformly deposited. This comes about through formation of a spray pattern by the nozzle tip; the most important element on the entire sprayer. The tip appears to be a simple mechanism, but the contrary is quite the case, particularly true of the commonly used fan pattern type. It is so complicated that, after years of investigation, Coulter and Dombrowsky report, «the hydrodynamics of this type of flow has not yet been fully analyzed».

It is believed improvement in tip pattern design is possible. Consequently, you the people of the user agencies should demand it. Sufficient to suggest is that full discussion of nozzle tip performances is too complicated a topic to undertake in this paper.

The hypothetically perfect compression sprayer may never be fabricated. Nevertheless marked progress in this direction has taken place. Through use of better materials and by improved design, weight has been reduced. Lighter elements fabricated from clear or tinted polythylene of polyvinylchloride plastics may be used in place of heavy metals in the lance assembly. Weight in the lance assembly alone has been reduced as much as 16 ounces by substituting plastics for metal parts. The cost of these materials is low, durability is excellent and transparent elements permit immediate supervision for cleanliness through out the house, the cutoff valve, and the lance. Furthermore the plastic elements may withstand more rugged field service than metal. A heavy vehicle may pass over a plastic lance without crushing or permenantly distorting it, where under similar conditions a bronze lance would be destroyed.

Reliable quick detachable units which depend upon O-rings for tight sealing are available. They may be used to connect all discharge line elements to each other and to the tank.

The pressure regulator has been a controversial element. Practically everyone agrees concerning its importance, but apparent failures have made it unpopular in instances. Experience usually indicated that the regulator is not faulty. Rather, it is not kept clean and clogs as a result. Reliability of this element has been increased considerably by improved design, but cleanliness still is of prime importance.

The operator has always been uncertain whether his nozzle tip pressure is correct. Frequently he has wrongly manipulated the pressure regulator in order to improve a hypothetical error in it. This problem is easily overcome by redesigning the regulator valve seat to function as a trickle valve. The trickle valve bypasses a small quantity of liquid when the cutoff valve is closed. In order to read the pressure on the tip, the pressure gauge must be relocated beyond the outlet port of the regulator, rather than in the conventional manner on the tank. Then, when the spraying operation is in progress, tip discharge pressure is registered on the gauge. When the cutoff valve is closed, sufficient liquid passes through the trickle valve to register residual tank pressure. Thus the gauge registers two pressures at practically the same instant.

The much maligned pressure gauge, which functions well when clean, has had something added to keep it clean. The addition is called a modified sylphon tube. This consists of a short piece of clear flexible polyethylene tubing. One end of the tubing is permanently attached to the intake orifice of the pressure gauge. After attachment, the entire gauge assembly — plastic tubing and Bourdan tube — is completely filled with a low viscosity liquid such as automobile brake fluid. The free end of the plastic tube is now closed by a suitable plug or other means. The modified gauge stem is attached in place on the tank and functions normally when pressure is developed. Thereafter no insecticide such as wettable D. D. T. can enter the gauge, clog the orifice, and bring about failure. An ingenious mechanic may make this installation on any sprayer equipped with a pressure gauge.

From time to time requests have been advanced to design an automatic shutoff valve which would interrupt liquid flow when tank pressure diminishes below the required pressure on the nozzle tip. Shutoff valve closure insures prompt repressurization, since spraying will remain interrupted until sufficient pressure is generated to reopen it. Such valves may now be obtained as standard equipment. One model incorporates the valve as part of the pressure regulator, opening and closing at the predetermined setting. Another type which performs the same function independently of the regulator, is being developed. Protypes appear to function well.

These elements represent a few of the recent modifications adaptable to compression sprayers. There are others but time does not permit discussion of them.

From the beginning the hand compression sprayer has been beset by one outstandingly obnoxious characteristic; frequent and laboreous need to be repressurized by the man in the field. In consequence, at least one rather revolutionary sprayer of the compression type, which completely eliminates hand pumping, has been developed. This sprayer has been redesigned from the nozzle tip to the method of pressurization. Prototypes function very well.

The polyethylene tank has a capacity of ten liters and is completely filled with liquid when fully loaded. There is no air filled dead storage space. The discharge pressure is regulated to 10 PSI through a pneumatically functioning pressure regulator, a distinct improvement over the hydraulic type regulator now commonly used, which had to cope with an insecticide in suspension. The plastic tank will withstand 25 to 30 PSI, allowing more than the reguired factor of safety of two.

A heavy duty cylinder, placed inside the tank in a manner similar to the familiar hand pump, contains propellant under high pressure. When recharging becomes necessary, a standby cylinder may replace the expended unit.

The reasonably simple mechanism is operated by manipulating one toggle lever which activates the various control valves, depending upon the position of the toggle. The cylinder is protected from over pressurization by a heavy duty safety valve.

Daily field operation proceeds as follows. The pressure cylinder has been charged at the central maintenance station and is taken to the field in normal position inside the plastic jar. In the field, the pressure cylinder is removed momentarily while the plastic jar is filled to capacity with insecticide. Then the pressure cylinder is replaced and secured in position by a plastic cap. The O-ring quick detachable lance assembly is snapped into position and the apparatus is ready to function. The toggle lever is moved to the proper position and spraying proceeds. When insecticide is exhausted, the toggle lever is returned to the neutral position and the plastic cap and pressure cylinder are removed. The jar is refilled with insecticide, closed, and spraying again progresses throughout the day .

The uncharged apparatus weighs about eight pounds and is designed to function at 10 psi tip pressure, the most economical to maintain. For higher pressures a metal tank may be substituted for the plastic jar.

Since no time is lost in frequent hand pressurizing, it is believed up to 75 percent more area may be covered per day, a very considerable saving in labor. Furthermore the workman may do a better job since he is not exhausted by the pumping operation.

The ideal pressurization method is by use of a solid propellant. Each charge will cost a few cents, U. S. A., a low price indeed per spraying day.

Freon 12 or 22 also may be used satisfactorily. Freon 12 is becoming readily available almost everywhere since it is an essential chemical in refrigeration and air conditioning. It costs somewhat more than the solid propellant, but is still less expensive than human labor when the increase in productive spraying is considered.

High pressure compressed air may be used but is probably not widely available. Initial air pressure should be at least 200 PSI, and several recharges will be required per day.

This self-activating sprayer has been designed, bearing in mind the malaria eradication point of view. The output of productive work should be consiberably higer than with the standard sprayer. Maintenance of the apparatus, particularly the often neglected cleaning chore, should be minimal. All plastic elements are highly resistant to distortion, corrosion and wear. Weight of the uncharged sprayer has been reduced over standard equipment. Initial cost should be competative with present equipment. Replacement parts are in-expensive and are readily installed.

MALARIA CONTROL ON WATER RESOURCE DEVELOPMENT PROJECTS: THE 25-YEAR EXPERIENCE OF TVA

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All over the world, technologic forces are today being marshalled in a giant effort to stamp out malaria. In the United States, this disease which once was a prominent cause of disability and death is now rarely seen. The southeastern part of the United States was the last area of our country on which malaria lost its hold. It is in the heart of this area that the multipurpose resource development project known as TVA (Tennessee Valley Authority) is located. The area of the Tennessee River basin is 41,000 square miles. It has an average annual rainfall of 52 inches, and the average annual flow from the river system is the highest of any river system of comparable size in the United States[2]. The average temperature during the summer season is generally 75° to 80° F., with maxima of the order of 105° F. The population of this region is approximately 3,500,000 and the surface area of the major TVA reservoirs is only slightly less than 600,000 acres. All of the ecological requirements for malaria transmission can be met in the Tennessee Valley (fig. 1).

Malaria was both endemic and epidemic in the southern United States from the early history of the settling of the North American continent. More recently, some twenty years before TVA was created by the U. S. Government, serious epidemic outbreaks of malaria occurred around some of the artificial impoundments constructed in the southern United States by other agencies for purposes of power production and

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[1] Director of Health, Tennessee Valley Authority, Chattanooga, Tennessee, U. S. A.

[2] Geological Survey Circular 44, May 1949, U. S. Geological Survey — Table 2.

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 368-377, 1959

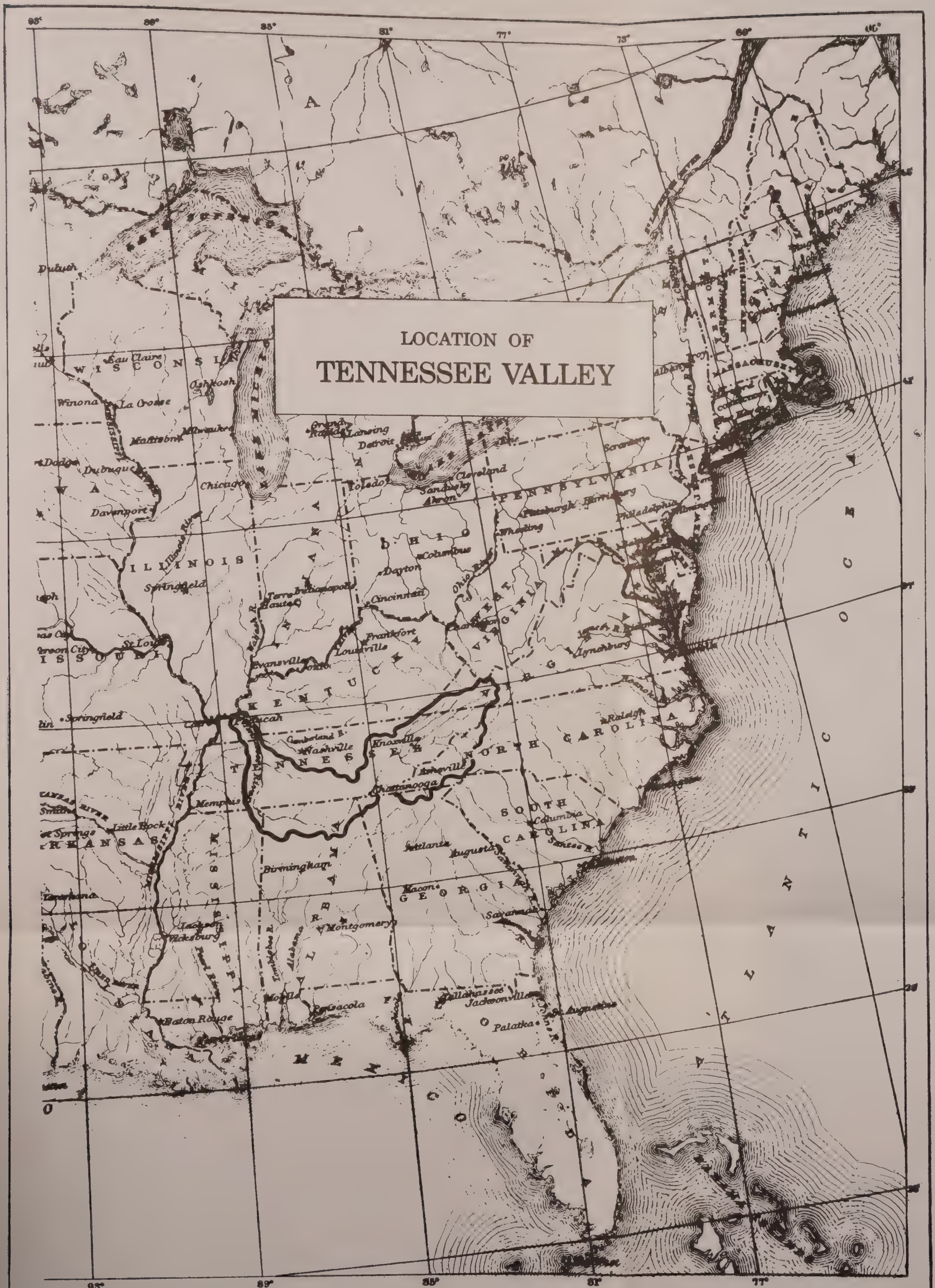
LOCATION OF
TENNESSEE VALLEY
93°
89°
85°
81°
77°
73°
69°
65°
Duluth
WISCONSIN
Eau Claire
Oshkosh
Winona
La Crosse
Milwaukee
Dubuque
Chicago
Davenport
ILLINOIS
Springfield
St Louis
MISSOURI
Springfield
Terre Haute
Indianapolis
Evansville
Louisville
Frankfort
Cincinnati
Dayton
Columbus
OHIO
Toledo
Detroit
Lansing
Grand Rapids
Cleveland
Sandusky
Akron
Wheeling
PENNSYLVANIA
Pittsburgh
Harrisburg
Philadelphia
Scranton
Albany
MASSACHUSETTS
Bangor
WEST VIRGINIA
Lynchburg
KENTUCKY
Paducah
Cairo
Cumberland R.
Nashville
Knoxville
TENNESSEE
Asheville
Chattanooga
NORTH CAROLINA
Raleigh
Memphis
Little Rock
ARKANSAS
SOUTH CAROLINA
Columbia
Atlanta
Augusta
Birmingham
Macon
GEORGIA
Savannah
Montgomery
Jackson
Vicksburg
Mobile
Pensacola
Tallahassee
Jacksonville
St Augustine
Palatka
Baton Rouge
ATLANTIC OCEAN

Fig. 1 — Location of Tennessee Valley

navigation[1]. In these instances malaria prevention and control did not receive adequate attention in the planning and operation of the projects. Subsequently it became necessary to take highly expensive corrective measures, even to the extent of draining or lowering some of the reservoirs, because the more prudent course of preventive planning had not been followed.

In 1933, the Tennessee Valley Authority was created as a Government-owned corporation with responsibility to achieve in the Tennessee River drainage basin and adjoining territory «the maximum amount of flood control, [...] the maximum development of the Tennessee River for navigation purposes, [...] the maximum generation of electric power consistent with flood control and navigation, [...] agricultural and industrial development, [...] reforestation, [...] the economic and social well-being of the people [...] and the maximum contribution to national defense». The combined story of all of these activities provides an example of resource development which is related to water control in many ways, for it is through harnessing and using water at a series of 31 major dams on one of the large river systems in the United States that much of the TVA program is accomplished (fig. 2).

Forewarned with knowledge of the relationships between ponded waters, *Anopheles quadrimaculatus* production, and malaria transmission, the Board of Directors of the Tennessee Valley Authority decided from the beginning «... that every possible effort will be made to maintain effective malaria control...» on the impoundments which would result from its extensive program of developing the Tennessee River and its tributaries. This basic policy decision was the keystone of the program for the prevention and control of malaria which was to follow. It signified that the mistakes made in the earlier development of water control projects by other groups were not to be blindly repeated. It meant that cause was to be sought out in advance of effects, and plans made to deal with cause in the design stages of TVA's work. It made clear that

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[1] «Impounded Water — Surveys in Alabama and South Carolina During 1914 to Determine its Effect on Prevalence of Malaria.» Carter, H. R., LePrince, J. A., and Griffitts, T. H. D. U. S. Public Health Service Bulletin 79, 1916. «Studies of an Epidemic of Malaria at the Gantt Impounded Area, Covington County, Alabama». W G. Smillie, *Am. J. of Hygiene*, vol. VII, n.° 1, 40-72, January 1927.

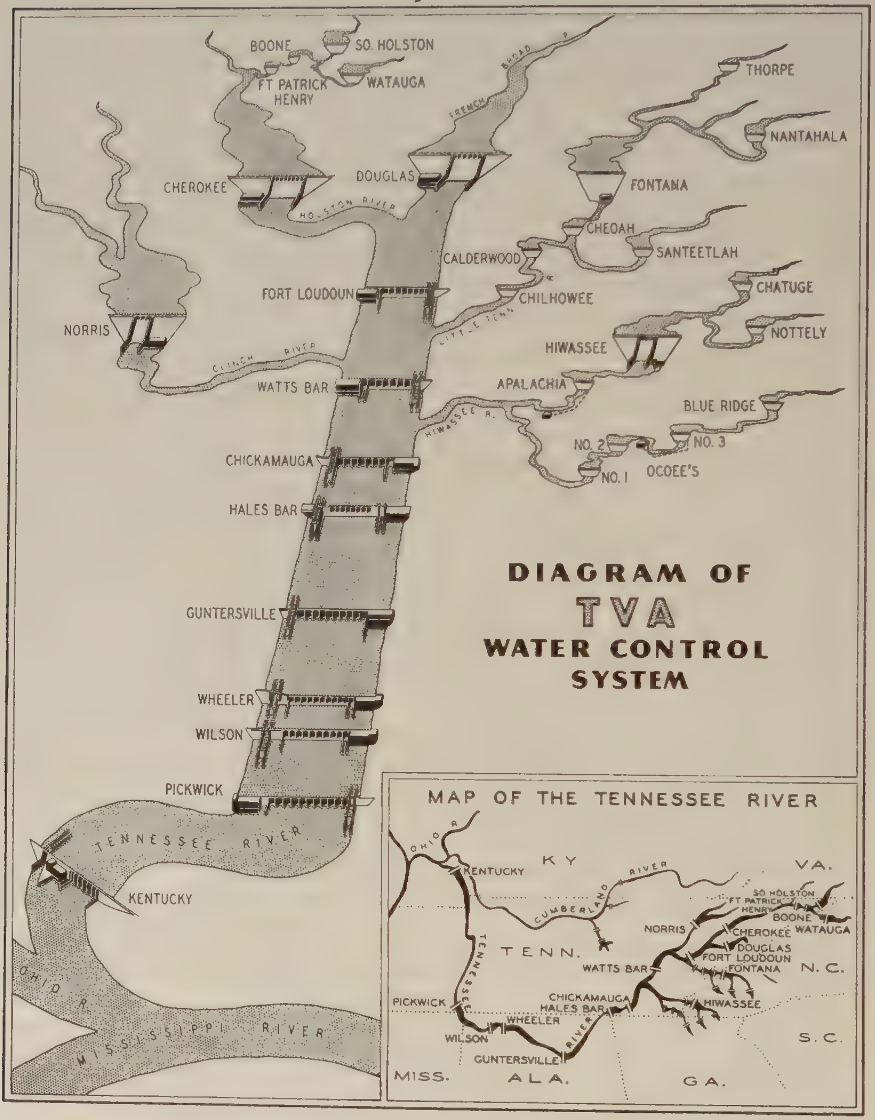
BOONE
SO. HOLSTON
FT PATRICK HENRY
WATAUGA
FRENCH BROAD R.
THORPE
NANTAHALA
FONTANA
CHEROKEE
DOUGLAS
HOLSTON RIVER
CHEOAH
SANTEETLAH
CALDERWOOD
CHILHOWEE
CHATUGE
FORT LOUDOUN
LITTLE TENN.
NORRIS
CLINCH RIVER
HIWASSEE
NOTTELY
APALACHIA
WATTS BAR
HIWASSEE R.
BLUE RIDGE
NO. 2
NO. 3
NO. 1
OCOEE'S
CHICKAMAUGA
HALES BAR
DIAGRAM OF
TVA
WATER CONTROL
SYSTEM
GUNTERSVILLE
WHEELER
WILSON
PICKWICK
TENNESSEE RIVER
KENTUCKY
OHIO R.
MISSISSIPPI RIVER
MAP OF THE TENNESSEE RIVER
OHIO R
KY
VA.
KENTUCKY
CUMBERLAND RIVER
SO HOLSTON
FT PATRICK HENRY
BOONE
WATAUGA
NORRIS
CHEROKEE
TENN.
DOUGLAS
FORT LOUDOUN
FONTANA
N. C.
WATTS BAR
TENNESSEE
PICKWICK
CHICKAMAUGA
HALES BAR
HIWASSEE
WHEELER
WILSON
RIVER
S. C.
GUNTERSVILLE
MISS.
ALA.
GA.
453K241

Fig. 2 — Diagram of TVA water control system

it was «the aim and purpose of the Tennessee Valley Authority to improve conditions in the Valley, not to create or maintain a health menace», and that malaria control was to be considered an essential in the program of water control to which TVA was committed.

In 1934, the malaria death rate in counties of the central section of the Tennessee Valley was 14.2 per 100,000 population, representing 37 deaths[1]. In 1934, a malaria survey of every fifth family out to the mile zone around future TVA reservoirs in roughly the same section of the Valley revealed a parasitaemia rate of 35 percent. Hence, the menace against which TVA determined to act was real and not imaginary.

Wherever successful and lasting malaria control programs have been developed and maintained, almost inevitably you will find those programs guided by a team which combines medical malariology, biology, and sanitary engineering. Responsibility for studying the TVA problem and developing and evaluating solutions was early placed in the hands of a small TVA staff group which included specialists in these fields. The decision by the TVA Board of Directors to make such an assignment of responsibility was the second key move in building the program for malaria prevention and control for the chain of TVA reservoirs. It gave substance to the basic policy decision earlier made by the Board by establishing a focal point for coordinating the work of many other staff groups throughout TVA in the tremendous job ahead. Thus the initial design of dams and reservoirs, though perfomed by the regular design staff, took into consideration the potential malaria problem and in advance provided physical features to make naturalistic control of mosquitoes possible through water level management after impoundage. And the pre-impoundage preparation of reservoir basins, though done by regular reservoir clearance crews, was carried out in accordance with specifications developed by the malaria control staff for eliminating marginal plant growth and for providing connecting channels between marginal depressions and the main body of the reservoirs. And after impoundment, operation of the reservoirs by water control engineers in achieving the over-all purposes of TVA has been carefully planned, with the malaria control staff furnishing advice and guidance concerning effects of water level management on mosquito production. Water control schedules necessarily are arranged for navigation, flood control, and power generation, but, consistent with these purposes, they are also devised so as to be of greatest possible advantage to mosquito control. Similarly, helicopters are needed for inspection of power transmission lines, but during the mosquito season, flying time needed for larviciding is given first priority (fig. 3). From these examples, it may be seen that the principal function of the malaria control staff is to develop, plan, and evaluate activities — an effective arrangement because the policy established by the Board of Directors not only prevented isolation of malaria control interests from other interests in project development but also assured collaboration between them.

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[1] Alabama Vital Statistics, 1934, Table 30.

The TVA malaria control program has been regularly and extensively documented and publicized from its beginning. Briefly, it is directed toward controlling the production of *A. quadrimaculatus*, the single vector of malaria in the region. To achieve this result, maximum use is made of naturalistic control potentials included in the initial planning of the many dams and reservoirs. Hence, reservoirs have been cleared and prepared to specifications in advance of impoundment, and shorelines are kept relatively free of marginal vegetation after impoundment; water levels are managed so that the major share of marginal plant growth control is accomplished by alternate flooding and dewatering which, at the same time, helps to produce an unsuitable micro-habitat for *A. quadrimaculatus*. This device (water level management) is the basic mosquito control measure on all 31 TVA reservoirs comprising more than 10,000 miles of shoreline, and on 24 out of the 31, it is the *only* control measure regularly employed (fig. 4). In seven reservoirs, D. D. T. larviciding by helicopter is used in selected areas where flat marginal terrain limits the effectiveness of water level fluctuations. These measures, in addition to a relatively small amount of plant growth control through herbiciding or machine cutting, and along with maintenance of marginal drainage systems and upkeep of dikes and pumps, are the principal features of the operational program for prevention and control of malaria which TVA now applies on its reservoirs. The program has been 25 years in the making and it has seen many new developments and changes. For example, the first larvicides were oil or paris green dust applied by knapsack or small boat, and water level management was first tried on only one — the smallest — reservoir on the main river stem. Now a highly complex pattern of inter-reservoir dis-

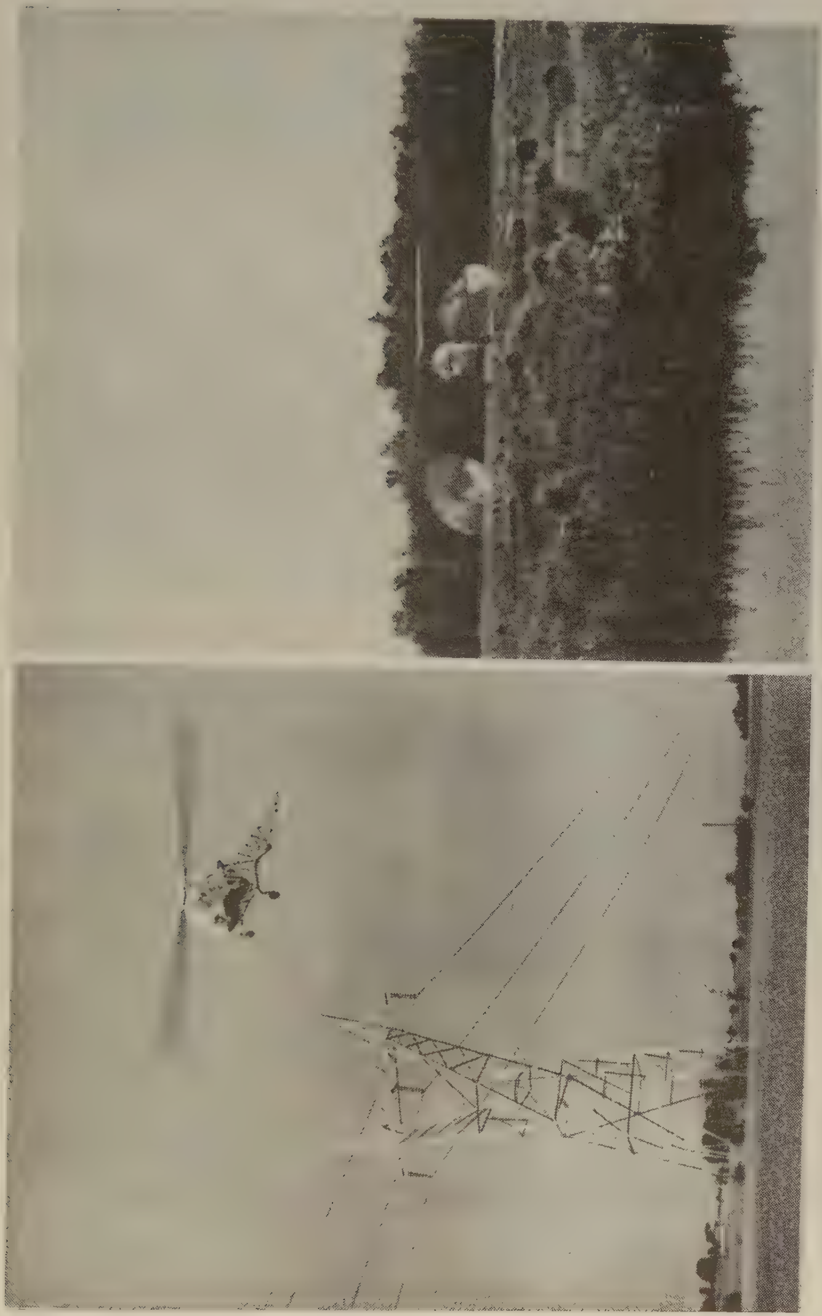

Fig. 3 — Joint use of helicopter for power line inspection and larviciding affords maximum year-round utilization of equipment

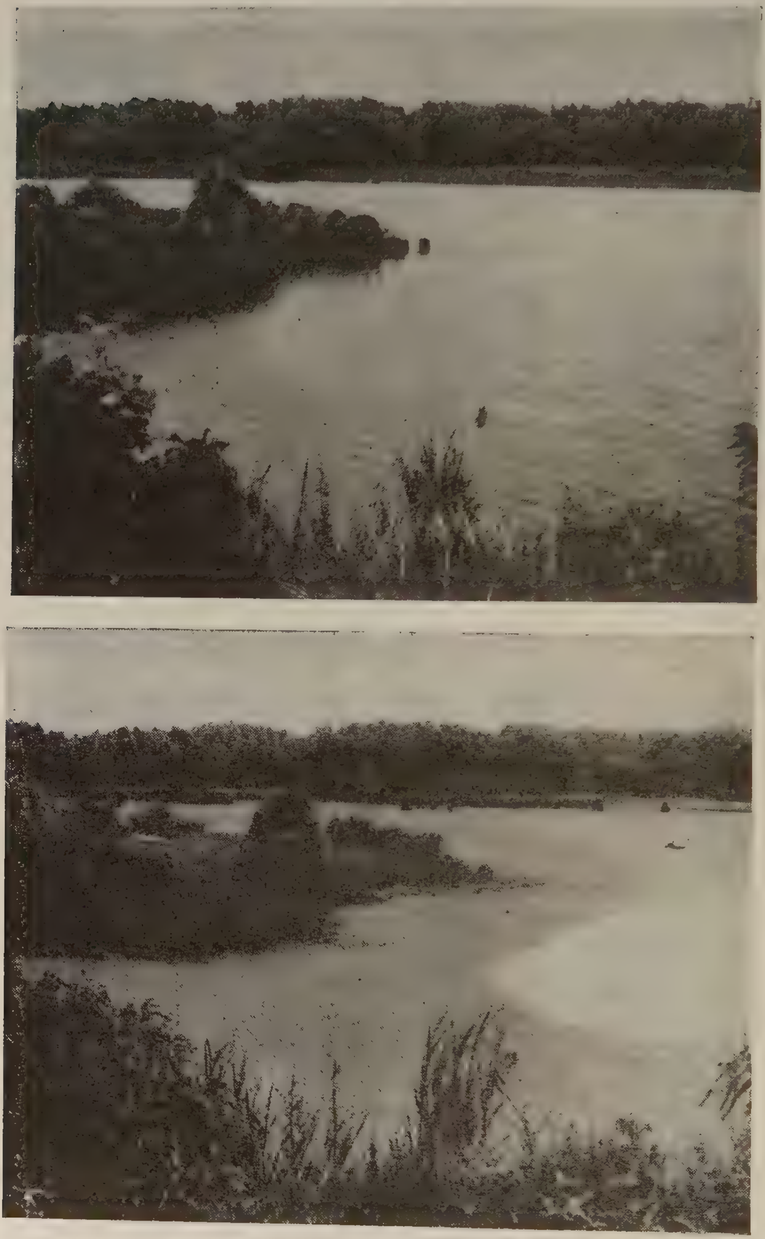

Fig. 4 — Appearance of shoreline at high and low water elevations of weekly fluctuation cycle

patching of water has been successfully established, and, though larvicides have been improved and methods of application revolutionized, dependence on them has been drastically reduced in relation to the increase of reservoir area. Once (1947) the annual program cost was nearly a million and a quarter dollars. Now the annual cost is only slightly more than 400 thousand dollars — despite the steady rise in labor and materials costs and the growing number of reservoirs.

We believe that clear assignment of program responsibility to a competent staff, together with the inter-discipline collaboration thus assured, has been the principal factor responsible for the sustained increase in program effectiveness and the simultaneous decline in program costs. Program planning by this group has been followed by careful program evaluation, and both have been supported by concurrent laboratory and field research. It was careful and continued field research which established the ecological relations of *A. quadrimaculatus* in our chain of reservoirs and thereby showed us what water level management would accomplish in the control of mosquito production, and it was field research which demonstrated that benefits would exceed capital costs of marginal cut-and-fill excavations and of selected diking which converted large acreages[1] from problem areas into areas where water level fluctuation would be effective (fig. 5). It was through a combination of laboratory and field research that we learned how to formulate and apply D. D. T. from airplanes and then from helicopters, and that we dispelled an earlier fear that *A. quadrimaculatus* in the Tennessee Valley might be developing resistance to D. D. T. And it is through continuing research in balance with carefully planned field operations that we hope to find even better and cheaper ways of maintaining effective control of mosquito production on our reservoirs.

In the Tennessee Valley area of the United States during the past twelve years, we have welcomed some 20,000 visitors from outside our country to see the program of multiple-purpose resource development which on May 18, 1958, celebrated its twenty-fifth anniversary. From some of these visitors we have heard exciting stories of ventures in

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[1] 9,099 Cut-and-fill
4,471 Diking and dewatering
13,570 Total acreage

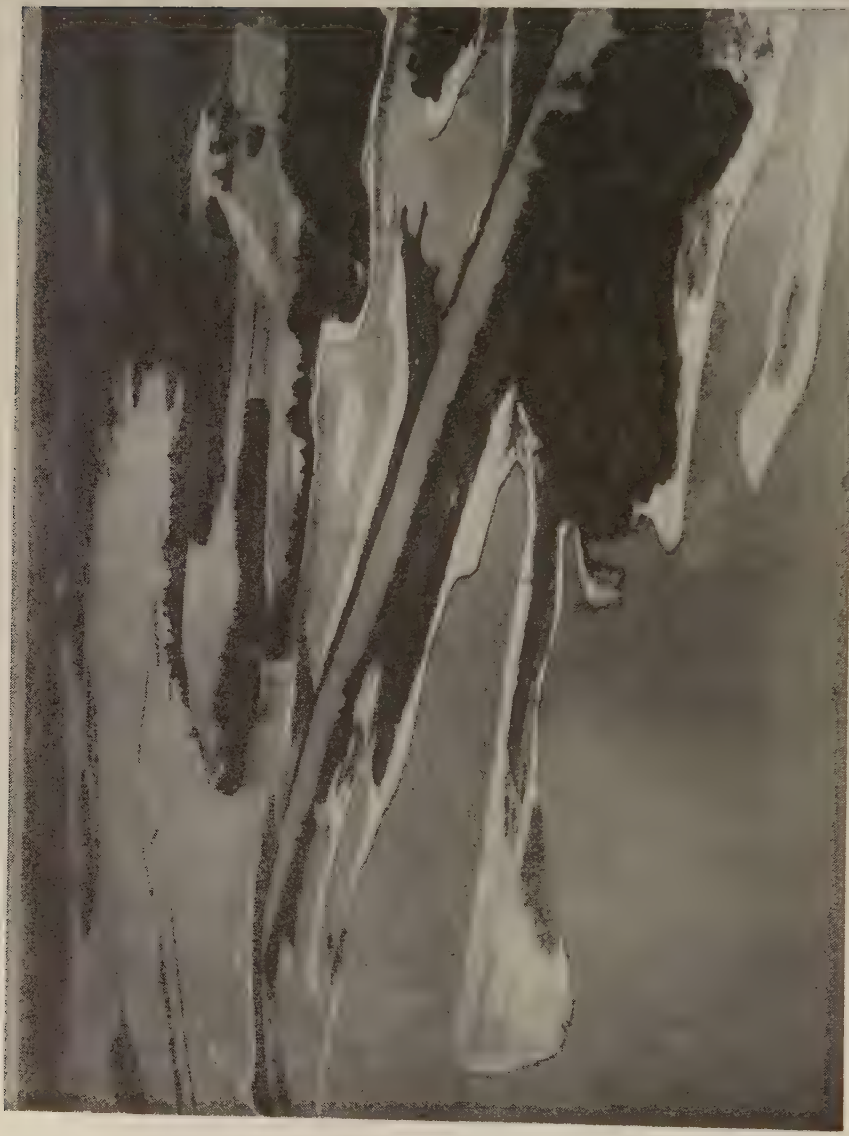

Fig. 5 — Reservoir margin changed by cut-and-fill to eliminate mosquito breeding areas

resource development being undertaken or planned elsewhere in the world which are similar in many respects to the program which TVA is carrying out. Artificial impoundment of water in areas where malaria is endemic carries with it a moral obligation to prevent or control conditions of impoundment which could result in the spread of the disease. In the Tennessee Valley Authority this threat was attacked at the source through making provisions for control of the insect vector of malaria, *A. quadrimaculatus*, utilizing naturalistic controls to the greatest extent feasible and combining them with selected supplementary control measures. We believe that such an approach, when feasible, offers greater promise of long-range prevention and control than complete or even major reliance on chemical poisons. And, in our experience, we have found no measurable resistance to chemical formulations which have been applied as a limited and supplementary method of control.

Applying this philosophy of *vector control at the source,* in TVA we have seen control costs decline, environmental hygiene improve, and malaria virtually disappear from an area of our country where once it was a serious health problem. Earlier I reported that a malaria survey in 1934 revealed a parasitemia rate of 35 percent. Since 1949, no case of indigenous parasitemia associated with TVA lakes has been discovered, despite the most careful continuing epidemiologic surveillance.

IMPORTANCE ECONOMIQUE DE LA LUTTE ANTIPALUDIQUE

M. Parent

Introduction.

La lutte contre la maladie, et spécialement la maladie endémique, a un double but: le premier, diminuer le nombre de victimes de cette maladie, c'est-à-dire, améliorer la mortalité et la morbidité de cette maladie; le second, de bonifier le standing de la population par l'augmentation des possibilités économiques du pays.

Celà est bien résumé par la doctrine du programme de la Santé Publique de l'Organisation Mondiale de la Santé: «Qu'ils aient la vie, et qu'ils l'aient pleinement.»

Dans le domaine spécial de la malariologie, on est convaincu de l'amélioration apportée par l'introduction des insecticides rémanants tant au point de vue mortalité et morbidité, qu'au point de vue amélioration du standing. Mais, jusqu'à présent, dans la littérature que nous avons consultée, nous n'avons trouvé que bien peu de données permettent de chiffrer réellement l'intérêt économique d'une lutte contre la malaria.

Citons, en guise de bibliographie, quelques renseignements glanés dans la littérature. Dans son livre *Géopolitique de la Faim,* Josué de Castro situe le problème du point de vue général (pages 47-48): «... Or, à l'heure actuelle, il existe dans le monde, selon les évaluations de l'Organisation Mondiale de la Santé, près de 300 millions d'individus atteints de paludisme, dont les bras affaiblis et fatigués ne se meuvent guère plus que pour porter la nourriture à leur bouche. Si le monde prenait la résolution d'en finir avec le paludisme, comme il l'a fait pour la fièvre jaune, nous pourrions compter d'ici peu sur 600 millions de bras de plus, capables de produire des aliments et de collaborer, de ce fait, à la lutte contre la faim. Les résultats partiels des campagnes de «dédétisation» qui ont assaini d'immenses régions de Grèce et du Brésil montrent qu'on peut constater une augmentation immédiate et spectaculaire de la production dans les régions libérées du fiéau.»

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 378-405, 1959

Dans la monographie de l'O. M. S. de 1952, *Le coût de la maladie et le prix de la santé,* Winslow passe en revue les divers aspects économiques de la maladie, et, comme cause de dépenses pour la maladie, citait:

1.° — Pertes économiques dues à la mort prématurée.

2.° — Pertes économiques dues aux maladies physiques et mentales.

Rappelons, en les citant, ces avis autorisés:

«A la perte en capital en vies humaines que cause la mort prématurée, vient s'ajouter la lourde charge imposée par les maladies que l'on peut éviter. Il s'agit d'une part de la perte de potentiel de production due à des maladies qui, sans être fatales, entraînent une incapacité de travail et, d'autre part, de l'accroissement des dépenses afférentes aux soins médicaux et hospitaliers nécessités de ce chef.»

Pour situer le problème, citons encore:

«Ailleurs, chaque été, les quatre cinquièmes de la population terrassée par le paludisme sont hors d'état de travailler...»

Et, dans le domaine africain, le même auteur rapporte:

«Le Docteur Morris, Secrétaire à la Santé de Rhodésie du Sud, a récemment signalé dans une communication adressée à l'O. M. S. que, dans son pays, le paludisme fait perdre de 5 à 10 % du total de la main-d'oeuvre disponible. La fréquence de cette maladie est d'aileurs la plus forte au moment où l'agriculture a besoin du plus grand nombre de bras.»

Quant aux résultats économiques obtenus, le même auteur, dans son chapitre 2. «Réduction des pertes économiques dues à la maladie: méthodes et résultats», cite pour l'Afrique, qui nous intéresse plus spécialement ici, les quelques chiffres recueillis dans le continent noir, entre autres dans l'île Maurice, où le chiffre de dépense par tête d'habitant est donné; ensuite, une expérience de Mac Donald sur des écoliers et une valeur pour des travailleurs:

«Pour des groupes typiques de travailleurs des cas de paludisme ont été constatés à raison de 22 à 183 attaques (ou rechutes) annuelles pour 100 personnes employées, chaque accès obligeant le patient à interrompre son travail pendant 3-4 jours.»

Cambournac donne une estimation du supplément de main-d'oeuvre nécessaire à cause de la malaria au Transvaal et au Natal. Cette valeur est de l'ordre de 30 % de main-d'oeuvre nécessaire au moins. D'autres chiffres nous viennent de régions d'Afrique du Sud. Ces valeurs donnent des approches à l'amélioration de l'économie du pays, soit en signalant que certains régions ont pu être exploitées grâce à la lutte par les insecticides rémanants, soit l'augmentation du prix des terres, soit par l'amélioration du rendement de la production, sucrière en l'occurence.

Citons en long deux observations:

«En Rhodésie du Sud, selon Blair, l'absentéisme atteignait 25 % environ pendant les moissons dans la vallée du Mazoe; or, le paludisme n'est plus maintenant qu'une cause d'absences négligeable dans la région traitée par le H. C. H.»; et:

«Dans la zône cuprifère (Copperbelt area) de la Rhodésie du Nord, les statistiques montrent que, pour un nombre comparable de mineurs occupés avant et après les travaux de drainage commencés en 1935, le total des journées de travail perdues, qui avait déjà subi une diminution sensible, n'était plus que de 2030 en 1945. En 1946, ces travaux prirent une nouvelle extension et l'on introduisit le traitement des maisons au D. D. T. En 1949, le nombre de journées de travail perdues était tombé à 270.»

Tel semble être l'aspect économique connu de la lutte contre la malaria.

Et, in fine, dans le chapitre «Rôle de l'O. M. S. en matière de recherches», Winslow écrit:

«*e*) Une autre tâche, plus délicate mais essentielle si l'on entend arrêter un programme rationnel, nous incombe encore: procéder à l'analyse détaillée des résultats obtenus dans la lutte contre des maladies déterminées, exprimée en termes du rendement économique effectif.»

Nous avons eu l'occasion d'étudier, dans un milieu bien défini, l'importance économique de la malaria. Cette observation a fait l'objet, en 1951, d'un premier travail publié dans les Annales de la Société Belge de Médecine Tropicale. Nous n'avions à cette époque que quelques quatre ans d'expérience. Nous présenterons ici des données portant sur huit ans d'action contre la malaria.

Nous écrivions dans ce travail quelques mots sur la position de l'hygiéniste dans son rôle de lutte contre la maladie:

«Remarquons une fois encore, la différence spécifique entre ces deux doctrines de la médecine: la médecine individuelle et la médecine sociale ou hygiène. Le rôle de l'hygiéniste est de juger sur des masses... La médecine individuelle fait, elle, appel à l'égoïsme des individus et pour celà a plus de facilité à convaincre des «clients» toujours prêts à voir soulager la souffrance. Et tant d'autres aspects séparent ces deux tendances.»

Ces idées restent vraies actuellement.

La maladie coûte cher à la Société, non seulement en perte d'individualités, mais aussi en pertes de travail et en manque à gagner. De plus, l'argent que l'on peut libérer d'une lutte contre une maladie permet d'affecter ces sommes à l'étude et à la solution d'autres problèmes, posés par d'autres maladies.

Et, pour terminer ce préambule, définissons notre position dans le travail que nous présentons: En nous basant sur des méthodes scientifiques et contrôlées, notre rôle consiste à mettre des populations à l'abri d'endémies et d'améliorer, non seulement les conditions de vie par la lutte contre la maladie, mais — et peut-être surtout — le standing de vie des populations par une augmentation de leurs possibilités énergétiques de rendement.

Ce dernier aspect du rôle de l'Hygiène a pour nous une importance primordiale dans nos pays africains.

Le milieu.

La communauté observée est composée d'agents européens et d'agents congolais, travailleurs d'une société minière.

Nous avons suivi, au cours des ans, une population de l'ordre de 2 000 agents européens qui, avec leurs familles, constituent un groupe de ± 6 600 personnes, et 20 000 agents congolais, soit avec leurs familles, à peu près 90 000 âmes.

Cette population est répartie en trois sièges principaux, sur une distance de 350 km.

C'est en juillet 1947 que les premières applications d'insecticides rémanants ont été faites, c'est en 1948 que cette méthode a été généralisée.

Avant 1947, des organisations antimalariennes existaient déjà: lutte antilarvaire, par épandage; distribution d'antimalariens (quinine-atébrine); drainages locaux; etc. Les résultats étaient très peu encourageants. Ces conclusions pouvaient être tirées par diverses valeurs statistiques, tenues soigneusement depuis 1933.

Disons aussi que la population considérée jouit pratiquement de la même organisation médicale. Même en changeant de lieu de résidence, la population reste soumise au même contrôle.

Nous pensons que les chiffres ci-dessous peuvent être considérés comme digne de foi et, plus spécialement, dans leur évolution au cours des ans.

Disons aussi que nous ne nous sommes pas souciés uniquement de «statistiques», mais que les divers contrôles classiques d'une lutte antipaludique ont été pratiqués: indices plasmodiques, détermination des vecteurs, indices d'infestation, enquêtes épidémiologiques, variation de la pullulation anophelienne, etc....

Nous ne voulons ici qu'examiner l'aspect économique de la lutte contre la malaria. Disons cependant rapidement un mot sur les techniques de lutte utilisées.

Les vecteurs de malaria dans la région examinée sont: *Anopheles gambiae* et *Anopheles funestus;* les autres espèces n'ayant jamais montré la présence d'infection malarienne dans les dissections.

C'est le *Plasmodium falciparum* qui est la forme de malaria pratiquement toujours rencontrée.

Nous avons dit en quoi consistait l'organisation de la lutte antimalarienne, avant 1947. En 1948, la lutte antimalarienne s'est augmentée de l'application de D. D. T. (poudre mouillable 50 %, ensuite 75 %), à la dose *de 2 grammes* de D. D. T. pur au mètre-carré, deux fois par an (technique: à la pompe type Hudson).

Les détails techniques de ces applications sont bien connus, nous ne nous étendrons pas sur le sujet.

Ces dernières années, quelques essais locaux ont été faits avec le H. C. H., la dieldrin, spécialement dans la lutte contre les mouches qui, comme dans le monde entier, sont devenues résistantes. Mais nous pouvons dire que l'insecticide de base dans la lutte contre la malaria est resté le D. D. T.

Les indices statistiques observés.

Comme nous le disions ci-dessus, nous possédions pour la communauté observée des chiffres statistiques depuis 1933.

Définissons d'abord ces valeurs:

1° — *La martalité par malaria:* ces chiffres correspondent en décès pour mille individus par cause de malaria ou hémoglobinurie. Ces valeurs donnés séparément pour les hommes, femmes et enfants? Nous entendons par enfant tous les individus âgés de moins de 15 ans.

2° — *La martalité infantile:* qui est le rapport entre le nombre de décès d'enfants de 0 à 1 an et le nombre de naissances-vie durant l'année sous examen. Ce chiffre est exprimé en pour mille.

3° — *La participation de quelques affections, dont la malaria, dans la morbidité totale:* la morbidité totale est exprimée comme suit: nombre de travailleurs soignés (internes + externes) pour cause de maladie ou accident en un an, divisé par le nombre de travailleurs moyen pendant l'année. Ce chiffre est exprimé en pour cent.

Participation en pour cent de la maladie:

$$\frac{\text{Nombre de cas de la maladie} \times 100}{\text{Nombre individus soignés (internes + externes) maladies seulement}}$$

Pour les femmes et les enfants, les accidents n'entrent pas en ligne de compte.

4° — *Nombre de journées perdues pour cause de malaria (européens):* avec la moyenne de journées perdues par agent par an: c'est le nombre total de journées perdues pour cause malaria, divisé par le nombre moyen d'agents.

6° — *Nombre moyen annuel de journées d'hospitalisation des femmes et enfants pour cause de malaria:* ce chiffre correspond au nombre de journées d'hospitalisation par malaria par an, divisé par le nombre de femme ou enfants.

7° — *La morbidité par malaria:* ce chiffre est donné, pour les européens et pour les indigènes (séparément hommes, femmes et enfants; ainsi que morbidité totale). Cette valeur correspond au nombre de cas de malaria divisé par le nombre des individus sous contrôle. Cette valeur est exprimée en pour cent.

Pour les européens, seule la morbidité totale est donnée.

8° — *Nombre moyen de journées perdues par cas de malaria pour les européens et nombre moyen de journées d'hospitalisation par cas de malaria pour les femmes et enfants de travailleurs:* cette valeur correspond à la division du nombre, soit de journées perdues, soit du nombre de journées d'hospitalisation par le nombre de cas dans chaque classe sous examen. Ce chiffre donne un aperçu de la gravité du cas de malaria.

9° — De plus, dans les divers tableaux qui vous seront soumis, nous donnerons les effectifs sous contrôle, tant pour les européens que pour les congolais.

Ces valeurs sont données dans les divers tableaux en annexe. La représentation graphique de 1946 à 1956 est donnée.

Les indices observés.

Ces indices peuvent être partagés en trois groupes:

1° groupe: données permettant de juger du standing général d'une population et nous *y* verrons l'influence de la mesure prise.

Ces données sont:

— Mortalité par malaria chez les enfants congolais;
— Mortalité infantile chez les enfants congolais;
— Participation de la malaria dans la morbidité totale.

2° groupe: ce sont des données qui peuvent se chiffrer facilement en monnaie du pays et qui permettent de montrer l'intérêt économique d'une mesure.

Ces chiffres sont:

— Nombre de journées perdues annuellement par les agents européens pour cause de malaria;
— Même valeur pour les travailleurs congolais;
— Nombre moyen annuel de journées d'hospitalisation des femmes de travailleurs pour cause de malaria;
— Même valeur pour les enfants de travailleurs.

3° groupe: données plus difficilement chiffrables directement, mais qui peuvent être estimées d'après les circonstances locales, ce sont:

— La morbidité par malaria chez les européens;
— La morbidité par malaria chez les congolais (hommes + femmes + enfants).

Comparaison des valleurs statistiques.

Dans chaque groupe nous avons comparé la valeur 1947 avec celle de 1956. Nous avons calculé, en prenant la valeur 1947 comme étant 100 %, à combien correspondait en % la valeur 1956. Cette valeur 1956, déduite des 100 % (1947), est, ce que nous appelons par la suite, le pourcentage d'amélioration.

A titre d'exemple de ce calcul, citons le calcul du % d'amélioration pour le nombre de journées perdues:

En 1947, le nombre moyen annuel de journées perdues par tête d'européen était de 1,60 $\left(\frac{1836}{1134} = 1{,}60\right)$, en 1956 cette même valeur est 0,07 $\left(\frac{132}{1887} = 0{,}07\right)$.

0,07 correspond à 4 % de 1,61 $\left(\frac{0{,}07 \times 100}{1{,}61} = 4\right)$ ce qui donne:

100 % (valeur 1947) moins 4 % (valeur 1956) = 96 % (pourcentage d'amélioration.

1^{e} groupe:

	Passe de	à	% amélioration
Mortalité enfants par malaria .... *Graphique n° 1*	4,25	0,10	98 %
Mortalité infantile .... *Graphique n° 2*	123,—	58,—	53 %
Participation malaria dans morbidité totale: Hommes	26,30	4,80	82 %
Participation malaria dans morbidité totale: Femmes	23,31	3,85	85 %
Participation malaria dans morbidité totale: Enfants .... *Graphique n° 3*	39,63	5,65	86 %

COMMENTAIRES

Ces améliorations situent dès le premier abord la question. Cette diminution est de l'ordre de celle constatée ailleurs. Notons, cependant, que l'amélioration de la mortalité infantile n'est pas uniquement fonction de la lutte contre la malaria, mais est fonction de différents facteurs d'hygiène de la femme et de l'enfant.

2° groupe:

	Passe de	à	% amélioration
Nombre moyen annual de journées perdues par malaria: Européens	1,60	0,07	96 %
Graphique n° 4			
Nombre moyen anual de journées perdues par malaria: Congolais	0,60	0,04	93 %
Graphique n° 5			
Nombre moyen annual de journées d'hospitalisation par malaria: Femmes	0,523	0,054	90 %
Nombre moyen annual de journées d'hospitalisation par malaria: Enfants	0,951	0,097	90 %
Graphique n° 6			

COMMENTAIRES

Dans la perte au travail, nous constatons une amélioration de 90 %. Ce gain est facilement chiffrable en monnaie, si l'on connaît le prix moyen de la journée de travail.

Une amélioration du même ordre est obtenue dans le nombre de journées d'hospitalisation des femmes et enfants. Cette valeur est aussi facilement chiffrable, d'après le coût d'une journée d'hôpital. De plus, et celà est une valeur non négligeable, un nombre important de lits est libéré pour utilisation dans la lutte contre d'autres maladies.

3° groupe:

Morbidité par malaria: Européens	46,4	3,96	92 %
» » » Congolais hommes	29,3	5,3	82 %
» » » » femmes	23,6	5,—	82 %
» » » » enfants	61,6	11,1	82 %
Total	40,7	8,3	80 %

Graphique n° 7

COMMENTAIRES

Ce troisième groupe, portant sur la morbidité par malaria, est plus difficilement chiffrable en monnaie. Il peut cependant être estimé, en tenant compte du coût des médicaments, du personnel médical, du manque à gagner, etc....

Divers: Gravité des cas de malaria: *graphique nº 8:*

Chez les européens, en 1947, un cas de malaria donnait une moyenne de 3,1 journées perdues.

En 1956, se chiffre est de 1,4 journées perdues.

Chez les indigènes, en 1947, la moyenne de journées perdues par cas de malaria est de 1,3 et en 1956, cette moyenne est de 0,8.

Sans vouloir épiloguer sur ces valeurs, nous pouvons cependant conclure que la malaria ne s'est pas aggravée.

Chez les femmes indigènes, la moyenne de journées d'hospitalisation en 1947 était de 2,2 alors qu'en 1956 ce chiffre est de 0,7.

Et, enfin, chez les enfants pour 1947 nous avions 1,5 journées d'hospitalisation par cas en moyenne. Ce chiffre en 1956 est de 0,8.

Nous constatons ici aussi que la malaria ne s'est sûrement pas aggravée à la suite de l'épandage de D. D. T.

Ces faits, croyons-nous, méritaient d'être constatés.

DISCUSSION ET CONCLUSIONS

Nous avons obtenu une diminution spectaculaire de l'incidence de la malaria, grâce aux insecticides rémanants. Nous avons pu, grâce à des indices nosologiques, donner un aperçu du gain économique obtenu par cette mesure.

Ce gain peut être facilement chiffré, compte tenu des prix de revient dans le pays ou la région sous contrôle.

Il est possible, avec les valeurs, d'estimer un budget de lutte en fonction des résultats économiques espérés.

Les améliorations obtenues sont de l'ordre de 90 % sur la situation existant avant l'introduction de l'insecticide rémanant.

Nous reprendrons les conclusions de VINCKE en 1951 *(Ann. Sté. belge Méd. Trop.*, tome XXXIII, nº 6, page 672):

«L'importance de la lutte antimalarienne au point de vue économique a été mise en évidence et il en résulte que dans le calcul du coût *per capita* il faut faire la balance entre le coût brut et le gain financier réalisé grâce à:

1.° — un meilleur rendement de la main d'œuvre
2.° — une diminution des absences
3.° — un désencombrement des hôpitaux
4.° — une meilleure utilisation de l'effort médical dans d'autres domaines.»

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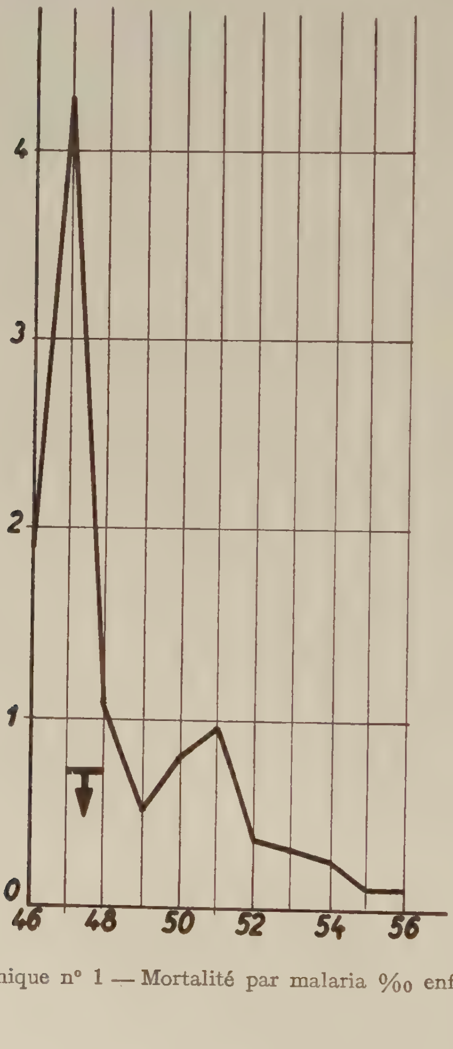
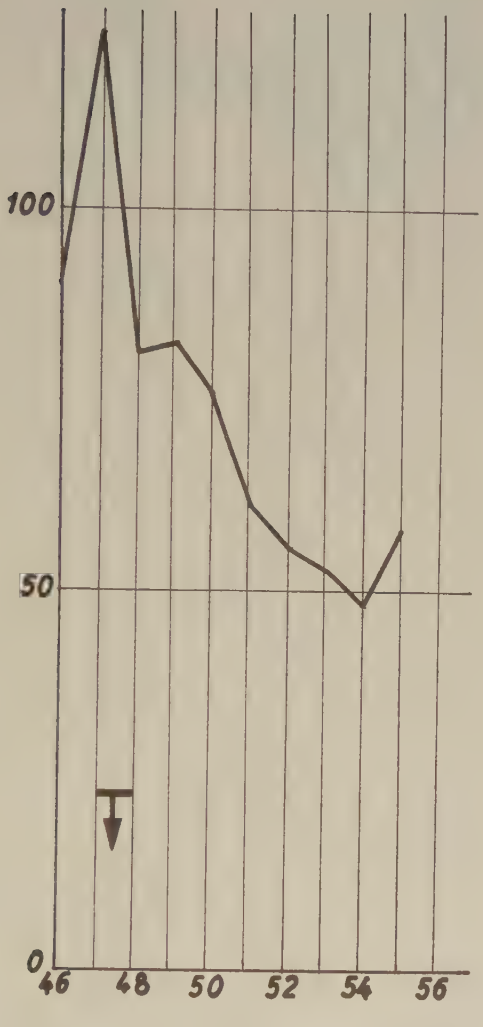
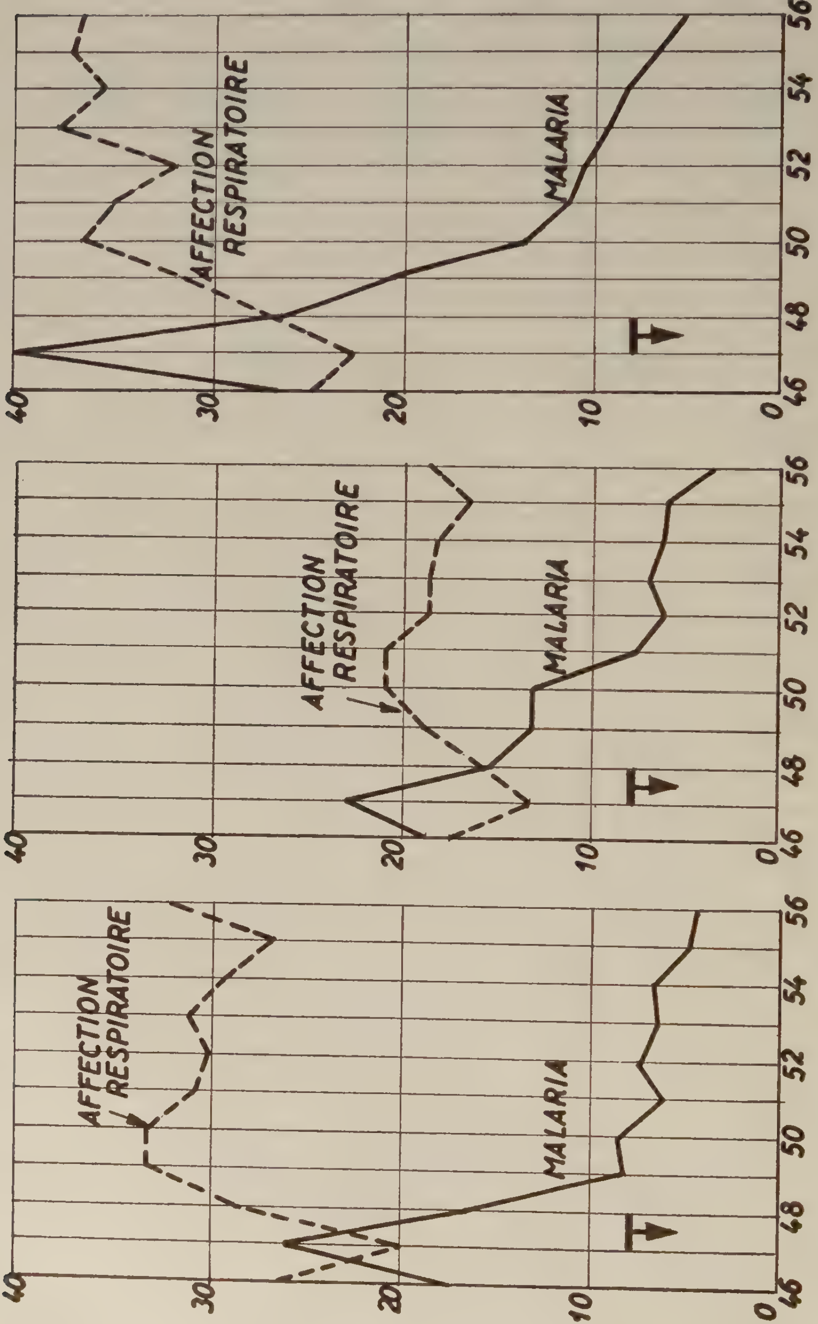


Graphique n° 1 — Mortalité par malaria ‰ enfants



Graphique n° 2 — Mortalité infantile ‰

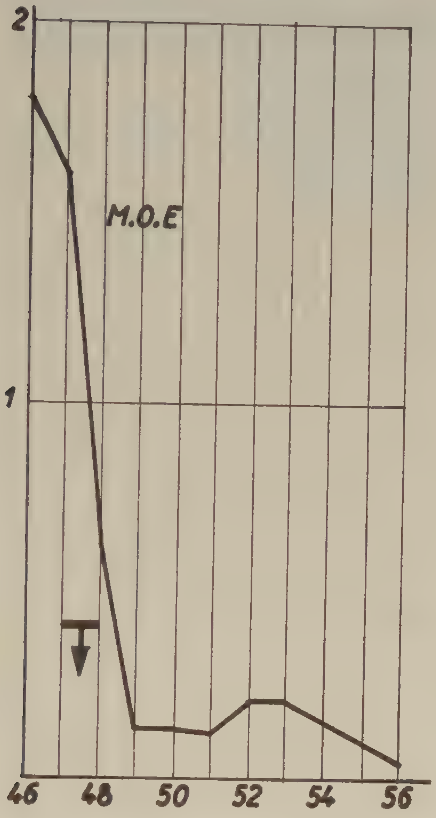


Travailleurs

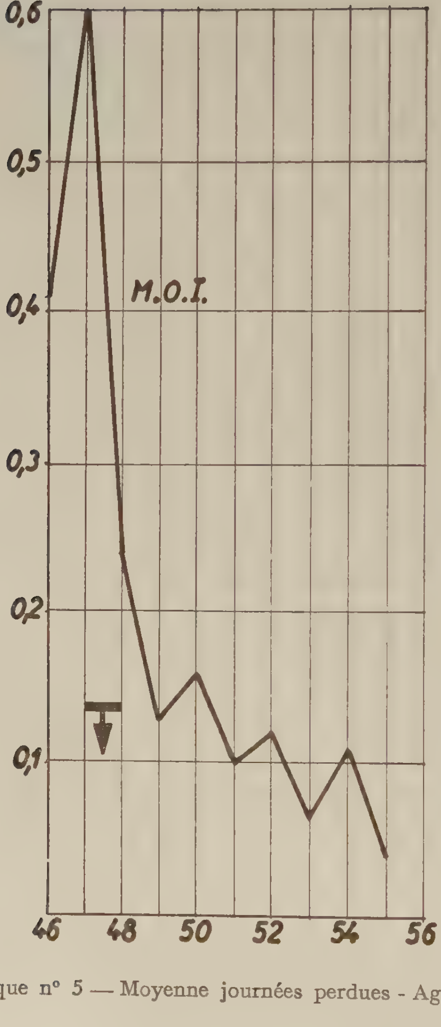
Femmes

Enfants

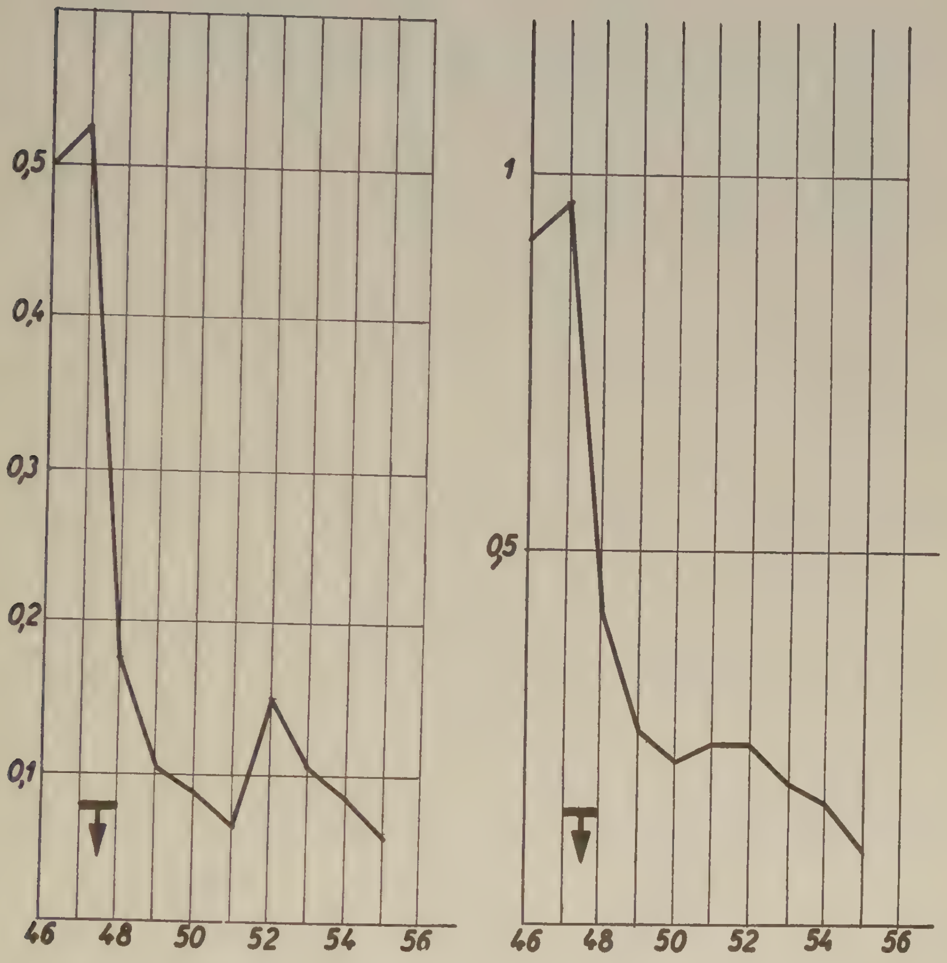
Graphique n° 3 — Participation % dans morbidité totale



Graphique n° 4 — Moyenne journées perdues - Agent - An



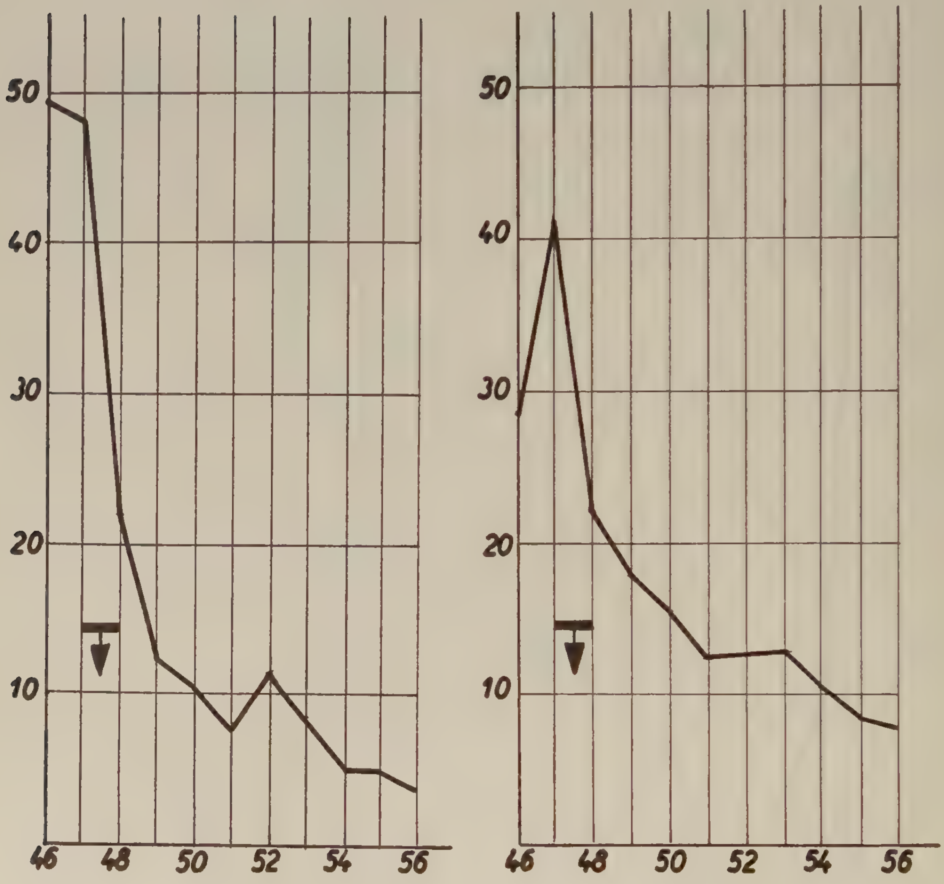
Graphique n° 5 — Moyenne journées perdues - Agent - An



Femmes

Enfants

Graphique n° 6 — Nombre journées hospitalisation - moyenne - An



Européens

Indigènes

Graphique n° 7 — Morbidité par malaria %

TABLEAU 1° — *Mortalité par malaria — Congolais* (Graphique n° 1)

Année	Mortalité par malaria pour mille			Mortalité maladie totale pour mille		
	Hommes	Femmes	Enfants	Hommes	Femmes	Enfants
1932	0,—	1,—	4,26	7,58	10,43	63,09
1933	0,23	0,—	5,28	5,14	10,53	44,71
1934	0,—	0,—	4,—	5,42	7,80	52,69
1935	0,—	0,—	3,74	5,45	4,96	55,64
1936	0,11	0,21	3,04	6,91	6,15	38,87
1937	0,—	0,—	2,22	8,42	5,83	42,87
1938	0,16	0,—	4,87	6,77	6,06	45,05
1939	0,—	0,—	3,89	3,67	5,49	38,47
1940	0,—	0,—	2,72	3,57	5,64	32,71
1941	0,07	0,—	2,65	5,—	4,25	27,70
1942	0,06	0,—	3,02	5,56	6,45	27,44
1943	0,10	0,24	3,19	5,16	5,98	31,47
1944	0,05	0,14	3,80	3,70	5,54	26,31
1945	0,—	0,—	3,04	3,29	4,81	22,18
1946	0,06	0,—	1,90	3,62	3,95	18,21
1947	0,—	0,—	4,25	2,11	2,93	26,63
1948	0,—	0,08	1,08	2,94	3,47	16,57
1949	0,—	0,—	0,53	2,61	4,40	15,14
1950	0,—	0,—	0,77	2,62	3,42	16,69
1951	0,—	0,—	1,17	2,47	2,22	13,69
1952	0,05	0,06	0,39	1,90	2,25	12,16
1953	0,—	0,—	0,31	2,06	2,72	11,56
1954	0,—	0,06	0,25	2,03	2,34	11,29
1955	0,—	0,05	0,10	2,24	2,32	11,47
1956	0,—	0,—	0,11	2,19	2,54	12,74

TABLEAU 2° — ***Mortalité infantile*** (Graphique n° 2)

Année	Mortalité infantile (pour mille)
1930	360
1931	266
1932	206
1933	185
1934	219
1935	210
1936	168
1937	215
1938	188
1939	149
1940	164
1941	101
1942	122
1943	112
1944	111
1945	112
1946	89
1947	123
1948	82
1949	83
1950	76
1951	61
1952	56
1953	53
1954	48
1955	58
1956	67

TABLEAU 3° — *Travailleurs* (Graphique n° 3) — *Participation en % de quelques affections, dont la malaria, dans la morbidité totale*

Année	Malaria	Affections respiratoires	Affections intestinales	Affections occulaires	Morbidité totale
1933	32,80	19,84	11,78	8,46	183
1937	21,40	21,90	15,90	7,50	171,8
1940	18,60	26,22	13,80	6,60	203
1943	14,30	27,37	17,01	8,45	207
1944	14,13	29,92	16,56	9,93	169
1945	14,—	30,50	13,10	10,58	169
1946	17,70	26,20	12,60	10,30	161
1947	26,30	24,10	10,20	11,20	146
1948	16,37	29,11	11,46	12,32	138
1949	8,39	33,84	12,17	10,68	140
1950	8,35	33,99	10,07	9,21	147
1951	6,41	31,45	12,21	9,73	145
1952	7,48	30,33	12,19	8,65	166
1953	6,83	31,21	13,54	7,81	165
1954	6,85	29,76	13,02	11,25	152
1955	5,12	27,53	12,07	11,54	145
1956	4,80	32,60	10,90	12,89	154

% de MORBIDITE

$$\frac{\text{Nombre de Travailleurs soignés Maladie} + \text{Accidents en un an}}{\text{Nombre de travailleurs}} \quad (\text{Int.} + \text{Ext.})$$

$$\text{Participation en } \% = \frac{\text{Nombre des maladies} \times 100}{\begin{array}{c}\text{Nombre travailleurs soignés (maladie seulement)} \\ \text{Internes} + \text{Externes}\end{array}}$$

TABLEAU 3° — *Femmes* (Graphique n° 3) — *Participation en % de quelques affections, dont la malaria, dans la morbidité totale*

Année	Malaria	Affections respiratoires	Affections intestinales	Affections occulaires	Morbidité totale
1933	25,98	5,53	5,34	12,65	98,20
1937	20.41	12,16	8,09	20,09	68,04
1940	16,34	17,73	9,10	17,05	117,—
1943	11,98	14,50	9,86	22,25	111,—
1944	15,93	14,93	0,28	18,31	100,—
1945	13,27	12,89	9,10	17,34	100,—
1946	18,20	17,40	10,50	17,—	110,—
1947	23,31	13,51	8,91	12,45	109,—
1948	15,46	15,05	8,91	11,18	112,—
1949	13,25	18,70	10,21	8,99	120,—
1950	13,38	20,57	8,70	7,96	125,—
1951	7,80	20,30	8,92	8,47	116,—
1952	6,10	19,15	8,56	7,45	129,—
1953	7,—	19,25	10,12	6,71	137,—
1954	6,41	18,59	9,98	8,82	133,—
1955	6,16	16,37	9,55	8,22	140,—
1956	3,85	18,29	8,25	—	138,—

Calcul:

$$\frac{\text{Nombre de cas soignés pour cette maladie en un an} \times 100}{\text{Nombre moyen de femmes}} \quad (\mathrm{I}+\mathrm{E})$$

TABLEAU 3° — *Enfants* (Graphique n° 3) — *Participation en % de quelques affections, dont la malaria, dans la morbidité totale*

Année	Malaria	Affections respiratoires	Affections intestinales	Affections occulaires	Morbidité totale
1933	33,41	14,21	8,18	20,15	233,80
1937	19,76	18,47	6,96	23,96	138,60
1940	23,71	30,84	6,36	15,94	216,—
1943	45,06	22,10	8,20	16,50	195,—
1944	28,20	24,45	8,97	15,61	177,—
1945	23,74	19,15	7,20	15,14	157,—
1946	27,10	24,90	8,60	16,10	173,70
1947	39,63	23,44	9,34	11,26	166,—
1948	26,47	27,11	11,06	16,01	143,—
1949	20,40	31,93	13,74	12,67	162,—
1950	13,30	37,62	14,74	11,58	177,—
1951	11,24	35,59	16,04	12,58	196,—
1952	10,25	32,12	15,88	10,83	205,—
1953	9,60	38,71	19,65	9,50	211,—
1954	7,88	36,—	21,27	12,45	196,—
1955	6,79	37,73	21,93	11,57	188,—
1956	5,65	37,05	21,20	—	218,—

TABLEAU 4° — *Européens* (Graphique n° 4) — *Nombre de journées perdues pour cause de malaria*

Année	Nombre de journées perdues	Moyenne par agent	Nombre moyen d'agents
1933	252	0,51	488
1934	191	0,34	550
1935	427	0,71	596
1936	247	0,39	625
1937	422	0,53	791
1938	495	0,56	875
1939	782	0,89	869
1940	599	0,65	925
1941	635	0,64	982
1942	940	0,92	1.018
1943	1.235	1,20	1.047
1944	2.026	1,90	1.080
1945	1.733	1,60	1.083
1946	1.834	1,80	1.005
1947	1.836	1,60	1.134
1948	784	0,62	1.265
1949	218	0,163	1.330
1950	202	0,153	1.327
1951	185	0,130	1.419
1952	330	0,200	1.615
1953	365	0,22	1.675
1954	252	0,15	1.676
1955	233	0,13	1.736
1956	132	0,07	1.887

TABLEAU 5° — *Congolais* (Graphique n° 5) — *Nombre de journées perdues pour cause de malaria*

Année	Nombre de journées perdues	Moyenne par agent	Nombre moyen d'agents
1933	2.945	0,687	4.281
1934	3.660	0,472	7.750
1935	8.789	1,000	8.787
1936	8.394	0,935	8.972
1937	7.552	0,662	11.400
1938	6.818	0,549	12.403
1939	8.142	0,696	11.686
1940	6.742	0,602	11.198
1941	6.453	0,482	13.382
1942	7.165	0,447	16.004
1943	7.749	0,391	19.783
1944	5.979	0,299	19.996
1945	5.097	0,284	17.900
1946	6.673	0,409	16.318
1947	9.369	0,600	15.613
1948	3.877	0,242	15.986
1949	2.048	0,129	15.707
1950	2.665	0,165	16.059
1951	1.683	0,099	16.972
1952	2.213	0,12	18.465
1953	1.561	0,07	19.425
1954	2.168	0,11	19.693
1955	961	0,04	20.969
1956	—	—	21.954

TABLEAU 6° — *Nombre de journées d'hospitalisation femmes et enfants, pour cause de malaria* (Graphique n° 6)

Année	Femmes	Enfants
1933	0,955	1,987
1934	0,677	1,814
1935	0,608	1,221
1936	0,500	1,155
1937	0,584	1,429
1938	0,353	1,097
1939	0,459	1,491
1940	0,570	1,311
1941	0,347	0,971
1942	0,357	1,060
1943	0,288	0,951
1944	0,318	1,004
1945	0,323	0,835
1946	0,501	0,911
1947	0,523	0,951
1948	0,179	0,415
1949	0,101	0,263
1950	0,090	0,224
1951	0,069	0,241
1952	0,151	0,236
1953	0,105	0,195
1954	0,087	0,158
1955	0,054	0,097

TABLEAU 7° — ***Morbidité par malaria*** (Graphique n° 7)

Année	Européens			Congolais			Total pour %
	Effectif H×F×E	Cas	Nombre cas %	Travailleurs	Femmes	Enfants	
1930	3.405	610	17,754	49,7	21,6	34,3	40,39
1931	2.695	577	21,41	49,2	22,0	27,3	37,80
1932	1.426	312	21,879	23,7	18,2	37,9	25,32
1933	1.051	254	24,167	24,5	22,2	58,8	31,91
1934	1.215	226	18,6	24,5	17,1	43,6	27,03
1935	1.323	289	21,844	31,0	10,2	19,8	23,14
1936	1.436	238	14,48	25,7	10,2	21,4	20,59
1937	1.779	284	15,96	18,0	10,3	22,3	16,88
1938	2.051	403	19,61	14,8	9,5	24,8	15.73
1939	2.142	542	25,1	20,7	12,8	34,3	22,03
1940	2.362	511	21,4	22,0	15,7	43,5	26.18
1941	2.484	531	21,4	25,7	17,6	40,1	28,59
1942	2.519	597	23,4	24,7	17,1	47,2	29,33
1943	2.675	673	24,9	20,5	13,3	45,3	26,18
1944	2.767	902	32,2	17,5	13,8	45,0	25,43
1945	2.746	945	34,14	17,6	13,3	37,3	23,45
1946	2.345	1.170	48,82	21,1	18,4	43,1	28,47
1947	2.864	1.329	46,4	29,3	23,6	61,6	40,70
1948	3.462	749	21,63	13,8	16,-	33,8	22,50
1949	3.696	469	12,69	8,5	14,7	29,0	18,80
1950	3.745	395	10,55	9,2	15,6	21,0	15,90
1951	4.143	319	7,70	6,7	8,3	19,6	12,80
1952	4.826	555	11,50	9,-	7,3	18,5	12,90
1953	5.097	460	9,02	8,3	9,-	18,-	13,-
1954	5.129	257	5,01	7,6	8,-	13,7	10,7
1955	5.394	273	5,06	5,5	8,1	11,3	9,-
1956	5.910	234	3,96	5,3	5,-	11,1	8,3

$$\frac{\text{Nombre de cas malaria} \times 100}{\text{Effectif moyen}} = \text{Morbidité \%}$$

TABLEAU 8° — *Nombre journées perdues ou journées d'hospitalisation par cas de malaria*

Année	Européens		Congolais		
	Nombre journées perdues par malaria moyenne agent	Nombre journées perdues par cas agent	Travailleurs journées perdues	Journées hospit.	
				Femmes	Enfants
1933	0,51	2,1	2,8	4,3	3,3
1934	0,34	2,0	2,7	5,0	4,6
1935	0,71	3,0	3,2	5,9	6,1
1936	0,39	2,8	3,6	4,8	5,3
1937	0,53	3,2	3,7	5,6	6,4
1938	0,56	2,8	3,7	3,7	4,4
1939	0,99	3,4	3,3	3,6	4,3
1940	0,65	3,0	2,7	3,6	3,0
1941	0,64	2,6	1,9	1,9	2,2
1942	0,92	3,3	1,8	2,1	2,0
1943	1,20	3,4	1,9	2,2	2,3
1944	1,90	4,5	1,7	2,3	2,2
1945	1,60	3,8	1,6	2,4	2,3
1946	1,80	4,0	1,9	2,7	2,1
1947	1,60	3,1	1,3	2,2	1,5
1948	0,62	2,5	1,8	1,1	1,2
1949	0,16	1,3	1,5	0,7	0,9
1950	0,15	1,6	1,8	0,5	1,1
1951	0,13	1,7	1,4	0,8	1,2
1952	0,20	1,6	1,3	2,-	1,1
1953	0,22	2,4	0,9	1,2	1,1
1954	0,15	3,1	1,4	1,0	1,1
1955	0,13	2,5	0,8	0,7	0,8
1956	0,07	1,4	—	—	—

TABLEAU 9° — *Population indigene*

Année	Hommes	Femmes	Enfants	Total
1930	16.340	6.773	4.457	27.470
1931	10.891	5.301	3.947	20.139
1932	4.616	2.971	2.108	9.695
1933	4.281	2.565	2.080	8.926
1934	7.750	3.612	2.790	14.152
1935	8.787	4.432	3.469	16.688
1936	8.972	4.712	3.936	17.620
1937	11.400	6.002	4.947	22.349
1938	12.403	6.933	5.950	25.286
1939	11.686	6.926	6.420	25.032
1940	11.198	6.464	6.604	24.266
1941	13.382	7.525	7.895	28.802
1942	16.004	9.443	10.566	36.013
1943	19.783	12.208	14.067	46.058
1944	19.996	13.367	16.040	49.503
1945	17.900	12.479	16.765	47.144
1946	16.318	11.887	17.301	45.506
1947	15.613	11.581	18.099	45.293
1948	15.986	11.802	19.305	47.093
1949	15.707	12.050	20.479	48.236
1950	16.059	12.555	22.045	50.659
1951	16.972	13.499	24.764	55.235
1952	18.465	14.647	28.120	61.232
1953	19.426	15.798	31.663	66.887
1954	19.693	16.221	34.895	70.809
1955	20.969	17.249	39.844	78.062
1956	21.954	18.477	45.195	85.626

LE PALUDISME AU VIET-NAM

Dr. PHAM-VAN-TRIEN

Le paludisme, fléau social majeur au Vietnam, cause une perte énorme en vie humaine parmi la population rurale et montagnarde, empêche la pénétration de la population deltaïque dans les moyennes et hautes régions, entravant ainsi le développement économique du pays.

A) CONDITIONS GEOGRAPHIQUES ET CLIMATIQUES.

La configuration géographique et les conditions climatiques du Vietnam jouent un rôle important dans la répartition du paludisme.

Nous en résumons les principaux caractères d'après les travaux de Bruzon, Carton et Romer.

Le climat du Vietnam est fortement influencé par l'orographie du pays. La partie septentrionale du Vietnam est constituée par des massifs et des hauts plateaux connus sous le nom de «Grande Cordillère», qui font suite aux hautes montagnes du Yunnan et du Kouangsi. Des cours d'eau importants les divisent, se dirigeant vers le Golfe du Tonkin. La *Grande Cordillère* se prolonge en direction NO-SE par deux chaînes de montagnes: l'une, demi-circulaire, se dirige vers le Thailand, l'autre s'incurve vers le Sud Vietnam par la *Chaîne Annamitique* (constituée en réalité par une série de chainons) qui dans sa partie la plus méridionale est prolongée par des *plateaux* dont les derniers contreforts se terminent à 120 km de Saigon.

La *Chaîne Annamitique* n'est pas une chaîne continue de grande hauteur mais une ligne plus ou moins large de 500 à 1 000 mètres d'altitude avec des pointements à plus de 2 000 mètres. Entre les pics élevés s'étendent de vastes plateaux à contreforts abrupts du côté de la mer de Chine, en pente plus douce du côté du bassin du Mékong (plateaux du Darlac, du Langbian). Cette disposition particulière de la *Chaîne Annamitique* s'allongeant parallèlement à la côte de la mer de Chine

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donne au climat du Centre Vietnam (ex-Annam) un caractère particulier très différent de celui du Nord et de celui du Sud.

Ce système orographique sépare deux grands bassins hydrographiques: celui du *Fleuve Rouge* dans le Nord et celui du *Mékong* dans le Sud. Les apports de ces deux grands fleuves et de cours d'eau de moindre importance forment des deltas reliés entre eux par une étroite bande de terre enfermée entre les pieds des montagnes et la mer (moins de 5 km de large à certains endroits).

Si influencés qu'ils soient par l'orographie, les facteurs déterminants du climat du Vietnam sont le régime des moussons et la latitude.

1.° — *Mousson.*

En rapport avec la mousson du Sud-Ouest on a, dans les deltas et à l'Ouest de la *Chaîne Annamitique* une saison des pluies (*grosso modo* de Mai à Octobre) et une saison sèche de Novembre à Avril. On passe de l'une à l'autre par une période de transition, de durée variable, que participe plus ou moins au régime de chacune d'elles. En rapport avec la mousson de NE on a, sur le littoral à l'Est de la *Chaîne Annamitique,* une saison des pluies d'Octobre à Février et une saison sèche de Mai à Septembre. Cette régularité dans le régime des pluies est toute relative, divers autres facteurs interfèrent avec les moussons.

En hiver, la grande masse des terres de l'Asie présent des températures extrêmement basses compte-tenu de la latitude et la pression y est très forte. Elle est alors le siège d'un fort anti-cyclone, à courant descendant, avec vent soufflant de la terre vers la mer, se joignant aux alizés. L'obstacle constitué par la *Chaîne Annamitique* fait que les pluies apportées par ces vents restent cantonnées à l'Est de cette chaîne.

En été, au contraire l'Asie centrale présente une température très élevée et la pression y est faible. Elle est alors le siège d'un grand mouvement cyclonique, à courant ascendant, avec vents soufflant de la mer vers la terre. Les alizés de l'hémisphère Sud sont entraînés vers le Nord puis déviées vers l'Est et forment la *mousson d'été* (ou de Sud--Ouest) apportant les pluies aux régions situées à l'Ouest de l'obstacle constitué par la *Chaîne Annamitique.* Au Sud de celle-ci, la mousson de SO est infléchie vers le Nord, puis vers le NO, apportant les pluies au delta du Tonkin. Cette mousson d'été, très régulière dans les régions du Sud Vietnam, est troublée dans le Nord par la formation de dépressions sur le Nord Vietnam, de durée, d'intensité et le siège variables.

En définitive, le région des précipitations est *grosso modo* le suivant:

Au Sud Vietnam (ex-Cochinchine) la saison des pluies débute dans la première quinzaine de Mai et se termine en Octobre, avec deux maxima l'un en Juin, l'autre en Septembre. De Novembre à Janvier les pluies sont rarissimes.

Au Centre Vietnam (ex-Annam) dans toute la zône littorale et dans celle des contreforts orientaux de la *Chaîne Annamitique* la saison des pluies débute en Septembre et atteint son maximum en Novembre ou Décembre et se termine à la fin de Janvier. Mais de Février à Septembre, se produisent des averses orageuses non exceptionnelles.

Au Nord Vietnam (ex-Tonkin et Nord Annam) la saison des pluises débute en Mai et se termine en Octobre avec un maxima en Août pour la région de Vinh. Les pluies se font plus rares en Novembre-Décembre--Janvier, après quoi intervient juqu'à la fin de Mars le «crachin» qui entretient l'humidité.

2.° — *Latitude.*

Les 1 620 kilomètres qui séparent les extrémités Nord et Sud du Vietnam sont compris entre 8° 31′ et 23° 22′ de latitude Nord.

Ce développement en latitude qui porte sur 15° (environ deux fois celui de la France) a comme conséquence d'importantes différences de température d'une région à l'autre. Il existe un hiver marqué dans le Nord alors que dans le Sud la température varie peu au cours de l'année. Là encore l'orographie intervient pour modifier cette condition générale.

Voici un apercu du régime des températures:

Le Nord Vietnam a un régime dont le trait frappant est l'irrégulier. Pendant la *saison chaude et humide* (Mai à Octobre) on enregistre dans la région deltaïque et dans les plaines de très fortes chaleurs (maximum signalé à Hanoi 42°,8 C en Mai), la moyenne des maxima la plus élevée étant 33°,2 C (Juin) et les plateaux de la Haute Région la température ne s'élève jamais audessus de 26° C. A la *saison sèche* et à la *saison du crachin* (Novembre à Mars) la temperature fraîchit très nettement. Il existe au Nord Vietnam un véritable *hiver* au cours duquel les moynennes mensuelles dans les plus basses régions oscillent entre 15° et 21° C (minimum observé à Hanoi + 5°-6° C). De courtes périodes de temps chaud (26°-28° C) se manifestent au cours de cette saison fraîche. Dans les régions de grande altitude et sur les plateaux l'hiver est plus accusé. Dans les postes militaires élevés du Nord Viet-nam, à la frontière de Chine, la température peut descendre parfois au-dessous de zero degré C (– 0°,9 C à LangSon, – 2° C à ChaPa). Ces fortes chaleurs et ces froids prononcés peuvent entraver l'évolution de l'hématozoaire chez l'anophèle comme ils peuvent aussi influencer la fréquence saisonnière des espèces (Toumanoff).

Le Centre Vietnam s'étendant beaucoup en latitude, présentant des plaines, des montagnes et des hauts plateaux, et subissant l'influence de la mer, doit être divisé en plusieurs régions:

a) *Région littorale.*

— Entre Donghoi et la Porte d'Annam, la *saison des pluies* (Août à Février) concorde ici avec la *saison fraîche*. La température varie de 15° C à 21° C. En *saison sèche* (Avril à Aoû) la température suit une courbe ascendente dès que cette saison est bien établie pour atteindre sa moyenne laplus élevée en Juillet (29° C),

— Entre la Porte d'Annam et le Cap Padaran la température est presque toujours haute. Elle sé'élève graduellement pendant la *saison sèche* (Février à Septembre) pour atteindre son maximum en Juin-Juillet-Août (maximum observé à Nha-Trang 39°,5 C en Juin). Pendant la *saison des pluies* (Septembre à Février) elle se maintient entre 24° et 28° C (minimum absolu observé à Nha-Trang 14°,6 C en Février). Les typhons qui sévissent au début de la *saison des pluies* sont plus accusés dans cette région qu'entre Donghoi et la Porte d'Annam.

b) *Régions des montagnes et des Hauts Plateaux.*

Sur toutes les montagnes et Hauts Plateaux de la *Chaîne Annamitique* les températures sont, à latitude égale, moins élevées que dans la région littorale du fait de l'altitude. La *saison fraîche* correspond ici avec la *saison sèche* (régime des régions à l'Ouest de la *Chaîne Annamitique:* Novembre à Mars). La moyenne mensuelle des minima la plus basse observée à Dalat étant de + 10° C (Février) et à Pleiku de + 12° C (Décembre) le minimum le plus bas relevé à Dalat est — 0°,6 C (Février) et à Pleiku + 5°,2 C (Janvier). La *saison chaude* se caractérise par une moyenne mensuelle des maxima la plus élevés de 26°,4 C pour Dalat (Avril) et de 30°,8 C pour Pleiku (Mai).

Le *Sud Vietnam* présent une absence presque complète de variations thermométriques entre la *saison des pluies* et la *saison sèche*. Les moyennes mensuelles sont toujours au-dessus de 25° C. Les mois les plus chauds étant Avril (moyenne 29°,8 C) et Août-Septembre (28° C), les plus frais en Décembre-Janvier (moyenne 26° C). Les températures extrêmes observées à Saigon sont 40° C (en Avril) et 16° C (en Décembre).

B) HISTORIQUE.

Le paludisme est connu depuis plus de deux mille ans dans le Sud-Est Asiatique et atenu une grande place dans l'histoire de l'Indochine. Nous en avons connaissance par les travaux archéologiques de l'Ecole Francaise d'Extrême Orient qui ont montré qu'à l'époque des civilisations locales, aujourd'hui entièrement disparues, la maladie avait été tenue en respect par de grands travaux d'assainissement (digues, canaux, etc....) exécutés dans des territoires actuellement insalubres et dépeuplés par le paludisme. Certaines légendes, qui datent de la plus haute antiquité, racontent que chez les habitants de la côte Indochinoise, les Vietnamiens en particulier, circulait la croyance que les anciens occupants, refoulés dans les montagnes, étaient de redoutables sorciers car ilspossédaient le pouvoir magique de fair périr de fièvre tous les ennemis qui osaient pénétrer dans leur domaine. Chez les habitants de la forêt, la légende est conservée de génies malfaisants qui vivent dans l'eau ou près de l'eau et qui s'attaquent aux hommes endormis, entraînant leur mort par une anémie progressive. De cette légende est resté le dicton de *l'eau mauvaise* appliqué généralement aux régions couvertes de forêts et aux Hauts Plateaux, zônes à forte endémicité palustre.

L'invasion chinoise des pays du Nord Vietnam a laissé dans les Annales sino-Vietnamiennes des renseignements plus précis et plus récents, signalés par les remarquables chercheurs Cordier et le R. P. Cadiere, collaborateurs de l'École Francaise d'Extrême Orient. Ces annales disent, entr'autres, que vers l'an 258 avant le Christ sous la dynastie de Tan, l'Empereur de Chine tenta de s'emparer du pays des Viet en envoyant une armée commandée par Do-Thuy. Les habitants se retirèrent devant l'ennemi et entrèrent dans la jungle. Ils se revinrent que lorsque les soldats de Do-Thuy furent «épuisés par le climat».

Plus tard, vers 1285, elles nous apprennent qu'au moment de l'apogée Mongole, Koubilai-Khan envoya son fils Togan châtier les Chams qui refusaient de reconnaître sa suzeraineté. Le droit de passage ayant été refusé aux troupes mongoles par le souverain du Tonkin et du Nord Annam, Tran-Nhan-Ton, ce dernier fut d'abord battu, mais au 5ème mois lunaire (Juin occidental) grâce aux premières pluies, les soldats mongols tombèrent malades de fièvre et ne purent résister aux nouvelles troupes levées par Tran-Nhan-Ton. Deux ans plus tard, une nouvelle tentative mongole échoua de la même façon. Le paludisme a donc probablement sauvé à plusieurs reprises le pays de l'invasion étrangère.

Plus près de notre époque, vers 1800, l'Empereur Gialong fit édifier dans tous les grands centres des citadelles à Vauban, entourées de douves profondes.. Ces constructions ont entraîné de véritables épidémies de fièvre palustre très meurtrières. L'hostilité séculaire du peuple à tous travaux de terrassement n'en a été que renforcée. Pour lui *le dragon* qui réside sous terre cherchera toujours à se venger et aujourd'hui encore, dans le Nord, c'est une entreprise redoutée que de risquer de *couper la veine du dragon*.

On pourrait croire de ce qui précède à une interprétation tendancieuse des textes par deformation professionelle du spécialiste si la localisation géographique et saisonnière des faits relatés ne donnait à cette interprétation une vraisemblance de réalité confirmée par les documents européens qui ne peuvent être taxés de faire partie du domaine de la légende.

L'histoire de Tourane rapporte les ravages faits par le paludisme parmi le corps de débarquement de l'Amiral Rigault de Genouilly en 1858. L'occupation du delta Tonkinois a été une surprise pour les médecins militaires qui ont exprimé leur étonnement de constater la rareté relative du paludisme dans cette région si marécageuse. En contre partie, les troupes en opérations dans le Yên-Thê région à eaux claires, subissaient épidémies sur épidémies. La situation sanitaire des troupes en garnison dans l'intérieur du pays n'était pas meilleure. Le paludisme constituait la cause de morbidité la plus importante et Grall indique que, d'Avril à Août 1885, sur douze mille hommes de troupes fraîches debarquées au Tonkin, un tiers de l'effectif succomba à la fièvre.

Terminons ce retour sur le passé en disant que dans le Nord, en 1897 (Serez), les hospitalisations pour paludisme dépassaient 50 % des entrées totales; qu'en 1903, à Laokay, la mortalité pour le paludisme atteignait le taux extrêmement élevé de 79 %, et que dans le Sud, en 1897 (Simond), dans le Binh-dinh, plus de 3000 décès par paludisme furent observés sur une population de 15 000 âmes.

La chaîne reliant le paludisme à l'anophèle, connue en théorie, ne paraissait pas encore évidante. Il revenait au Dr. Noel Bernard, Directeur de l'Institut Pasteur de Saigon, l'honneur, en 1919, d'en établir l'authenticité et, relation de cause à effet, de faire les premières grandes expériences de prophylaxie anti-palustre en Indochine.

Le rush des plantations en 1926, dans le Sud, amena une poussée de paludisme et la mortalité atteignit 84 % parmi la main d'oeuvre agricole. L'application des mesures de prophylaxie, dont les expériences conduites par l'Institut Pasteur de Saigon venaient de montrer la valeur, enraya aussitôt cette poussée.

C) STATISTIQUES CONCERNANT LE PALUDISME.

Le paludisme prend la première place parmi les différentes maladies atteignant la population Vietnamienne, bien avant la tuberculose, les dysenteries, le choléra (en dehors des épidémiees); la variole, la syphilis, etc....

Morin, en 1926, estimait à 2 millions le nombre de sujets atteints par le paludisme sur une population de 20 millions d'habitants. Mais comme le fait F. Dy, il faut tenir compte que 14 à 15 millions d'habitants peuplent les riches deltas du *Fleuve Rouge* et du *Mékong,* de telle sort que les 1 à 2 millions de malades se répartissent presque uniquement sur 4 à 5 millions d'individus résidant dans les régions paludéennes, soit environ 40 à 50 % de la population.

Vaucel indique, d'après de récentes statistiques, que l'Indochine totalise 1 300 000 consultants annuels pour paludisme et que 20 % de la mortalité générale s'y rattache.

Les progrès réalisés en Indochine dans la lutte antipalustre jusqu'à la seconde guerre mondiale ressortent des chiffres des statistiques officielles. Pour citer quelques uns de ceux-ci, le taux de morbidité général par paludisme est passé de 500 pour mille en 1904. De 1905 à 1930 il oscillait entre 180 et 250 pour mille. Mais parmi les rassemblements de main d'oeuvre il demeura longtemps plus important: en 1928, sur les plantations, le taux des décès par paludisme atteignit en certains points 400 pour mille.

En 1940, le nombre d'hospitalisations pour paludisme dans les formations de l'assistance médicale était de 138 pour mille hospitalisations et les décès au cours de l'hospitalisation de 190 pour mille décès, selon la répartition suivante:

	Hospitalisations (pour mille)	Décès (pour mille)
Fièvre (accès palustre)	115	52
Cachexie	19	83
Accès pernicieux	4	55

Pendant la seconde guerre mondiale, la raréfaction des produits antimalariens amena, pour 1943, les résultats ci-après: 196 pour mille hospitalisations et 215 pour mille décès au cours d'hospitalisations, soit:

	Hospitalisations (pour mille)	Décès (pour mille)
Fièvre (accès palustre)	162	77
Cachexie	29	77
Accès pernicieux	5	61

D) EPIDEMIOLOGIE GENERALE.

1° — *Le parasite.*

Les trois principaux types d'hématozoaires sont représenté en Indochine, nous en verrons plus loin la répartition suivant les régions.

2° — *La transmission.*

Dans le domaine entomologique de nombreuses espèces anophéliennes ont été décrites. En Indochine, et au Vietnam en particulier, les recherches du Dr. Borel et de ses successeurs ont permis d'identifier 25 espèces énumérées ci-après[1]:

Groupe «Anophèles» *sensu stricto*

A. aitkenii, James.
A. barbirostris, V. de Wulp
A. gigas var. baileyi, Edwaeds
A. hyrcanus var. sinensis, Wiedeman
A. hyrcanus var. nigerrimus, Giles
*A. lindesayi,*Giles
A. annandalei interruptus, Puri
A. alongensis, Venhuis
A. baezai, Gater

Groupe «Myzomyia»

A. aconitus, Donitz
A. culicifacies, Giles
A. jeyporiensis, James
A. jeyporiensis candidiensis, Koidzumi
A. minimus, Théobald

Groupe «Pseudo-myzomyia»

A. vagus, Donitz
A. subpictus, Grassi
A. ludlowi var. sundaicus, Rodenwaldt

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[1] Voir la carte donnée en annexe.

Groupe «Neocellia»

- *A. fuliginosus,* Giles
- *A. karwari,* James
- *A. maculatus,* Théobald
- *A. maculipalpis var. indiensis,* Théobald
- *A. philippinensis,* Ludlow

Groupe «Neomyzomyia»

- *A. kochi,* Donitz
- *A. leucosphyrus,* Donitz
- *A. tesselatus,* Théobald

Les travaux de Gaschen, Raynal et Toumanoff sur l'infection naturelle des anophélinés ont permis de classer ces 25 espèces en:

— Vecteurs majeurs
— Vecteurs secondaires ou mineurs
— Espèces banales

Vecteurs majeurs:

- *A. minimus*
- *A. jeyporiensis*
- *A. ludlowi var. sundaicus*

Vecteurs secondaires ou mineurs:

- *A. aconitus*
- *A. maculatus*
- *A. leucosphyrus*
- *A. hyrcanus var. sinensis*
- *A. subpictus*

Espèces banales:

Parmi les espèces banales citées ci-après ont été trouvées infectées:

A. culicifacies
A. hyrcanus var. nigerrimus
A. karwari
A. kochi
A. tesselatus et
A. vagus

La rareté des cas d'infection rencontrés laisse supposer que ces six dernières espèces ne jouent qu'un rôle accidentel dans la transmission du paludisme du Vietnam.

E) REPARTITION DU PALUDISME AU VIETNAM.

La démographie au Vietnam est commandée en grande partie par la distribution du paludisme. Au Vietnam, les régions montagneuses et des Hauts Plateaux ont encore une population très clairsemée, le paludisme règne en maitre empôchant l'exploitation de terres parfois très fertiles. L'examen des enfants nés sur place y brosse un tableau saisissant du paludisme fléau social. Par contre les régions deltaîques, en général plus saines, accusent plus de dix mille habitants au kilomètre carré.

Les aspects multiples du problème du paludisme nous ont conduit à différencier les terres saines et les terres à paludisme, à classer les emplacements larvaires anophéliens en gîtes permanents et en gîtes résiduels. Ces situations ont été réparties par Toumanoff en six sites:

Site 0: Région maritime basse ou littorale. Plages. Lais de mer. Côte d'altitude parfois inférieure au niveau de la mer.

Site 1: Zône deltique proprement dite. Eaux douces. Rizières basses, cours d'au lents et boueux.

Site 2: Zône intermédiaire dite *des terrasses*. Les accidents de terrain permettent la construction de ruisseaux plus ou moins rapides. Fossés des citadelles.

Suite 3: Zône de mamelons franchement accusés. Très richement irriguée en général par des cours d'eau rapides. Région des Plantations.

Suite 4: Zône montagneuse et des hauts plateaux, avec rizières étagées à eau courante. Cours d'eau très rapides. Emergences.

Suite 5: Zône de haute altitude proprement dite. Vallées profondes. Cours d'eau torrentiels. Ruissellement abondant.

Cette répartition et les variations épidémiologiques nous amènent à considérer un certain nombre de situations malariologiques aux caractères nettement tranchés, que nous allons décrire par ordre d'importance paludéenne et économique, conjointement:

A — Paludisme des régions accidentées de basse et moyenne altitudes.
B — Paludisme des zônes montagneuses.
C — Paludisme du littoral ou paludisme des zônes maritimes.
D — Paludisme des deltas.
E — Paludisme de haute altitude.
F — Paludisme d'importation.

(Voir tableau I *in fine* schématisant ces situations.)

1.° — *Paludisme des regions accidentees de basse et moyennes altitudes*

Ces régions, comprises dans les «sites 2 et 3», correspondent géographiquement d'après Gourou à:

— Région des *terrasses,* alluvionnaires anciennes, où les accidents des terrains permettent la formation de ruisseaux et parfois d'émergences;

— Région de basses montagnes, mamelons franchement accusés, abondance de cours d'eau très actifs en toute saison.

Cette zône comprend en presque totalité:

— Toutes les exploitations agricoles telles que plantations de thé, café, laquier, etc., dans le Nord; et d'hévéas, abrasins, et., dans le Sud.

— La majorité des centres urbains et des travaux d'irrigations dans le Nord.

— Quelques situations exceptionnelles telle que celle des citadelles du centre et du Nord Vietnam. Régions très peuplées, à très forte densité humaine en certains points.

Les indices endémiques y sont assez élevés:

— Indice splénique de 20 à 35 %;
— Indice plasmodique de 15 à 45 %;
— Indice gamétique de 5 à 10 %.

En certains points ils s'élèvent respectivement à 60 %, à 80 % et 100 %, et à 15 %.

L'étude des variétés d'hématozoaires montre la grande fréquence des infections à *Plasmodium falciparum,* dont le normbre croît avec l'âge, tandis que celle à *Plasmodium vivax* tendent à décroître lentement. Le *Plasmodium malariae* dont les infections sont beaucoup plus rares dans le jeune âge, voit son taux s'accroître progressivement et atteindre chez l'adulte celui du *P. vivax.*

Par ailleurs les variations saisonnières des hématozoaires sont très différentes entre le Nord et le Sud.

Dans le Nord:

P. falciparum a une recrudescence saisonnière nette qui se produit pendant les mois d'hiver (Novembre, Décembre, Janvier et Février) et une chute brutale toujours située au mois d'Avril.

La courbe saisonnière de *P. vivax* s'oppose de facon frappante à celle de *P. falciparum* par une incidence très marquée au début de la saison chaude et pendant cette saison chaude (Avril, Mai, Juin, quelquefois Juillet).

P. malariae n'a pas de courbe saisonnière, son taux est constant pendant tous les mois de l'année.

Dans le Sud:

P. falciparum, à l'inverse de ce qui se passe dans le Nord, a une augmentation d'insensité en Juillet, Août et Septembre, saison des pluies.

P. vivax suivant la même inversion voit son taux s'accroître au début de la saison sèche (Octobre) avec un clocher très marqué en Décembre.

P. malariae, relativement rare, varie peu tout en ayant une légère recrudescence vers la fin de la saison sèche (Avril, Mai).

L'étude comparative des indices splèniques et plasmodiques montre qu'ils se maintiennent à peu près à un taux identique jusqu'à 8 ou 9 ans. Au-dela, les indices spléniques deviennent nettement supérieurs aux indices plasmodiques.

Les relations entre l'âge, la forme parasitaire et l'hypertrophie splénique montrent:

— Qu'à tout âge, le pourcentage des splénomégalies chez les porteurs de *P. malariae* est très nettement supérieur à celui qu'on observe dans les autres variétés;

— Que, chez les porteurs de *P. falciparum*, la proportion des splénomégalies est plus faible dans les premières années pour s'élever ensuite d'âge en âge à partir de 5 ans;

— Que, chez les parasités par *P. vivax*, la proportion des splénomégalies est plus forte dans les premières années de la vie pour diminuer nettement ensuite, étant de très loin dépassée par *P. falciparum*.

Dans ces régions, les formes graves du paludisme: accès pernicieux et fièvres bilieuses hémoglobinuriques frappent l'Européen et les Vietnamiens qui s'y aventurent.

Les captures des espèces anophéliennes dans cette zône permirent d'identifier:

A. minimus, *A. jeyporiensis*, *A. maculatus*, *A. aconitus* *A. sinensis*, *A. vagus*, *A. barbirostris*, *A. fuliginosus*, *A. philippinensis*, *A. maculipalpis*, *A. kochi*, ainsi que *A. aitkenii*, *A. karwari* et *A. tesselatus* relativement rares.

A. minimus a un pourcentage de fréquence nettement supérieur à celui des autres espèces (80 %).

A. jeyporiensis venant ensuite.

A. hyrcanus var. sinensis étant plus largement représenté que *A. vagus*.

Cette pullulation est en rapport avec les gîtes rencontrés: ruisseaux à eau claire, à cours assez rapide et bords herbeux; mares à eau claire renouvelée, végétation aquatique et bords herbeux; marécages alimentés par des infiltrations d'eaux de sources; rizières à eau courante; creux de rochers aux bords des rivières et ruisseaux; forment les gites types où l'on rencontre les deux espèces les plus dangereuses *A. minimus* et *A. jeyporiensis*. Les dissections des femelles adultes de *A. minimus* capturées montrent qu'il est l'espèce rencontrée infectée naturellement dans la plus forte proportion:

A. minimus: de 1,56 à 3,69 %.
A. jeyporiensis: 1,00 %.
A. aconitus: 0,65 %.
A. vagus: 0,025 %.

Au point de vue saisonnier: *A. minimus,* dans le Nord comme dans le Sud, a son maximum de pullulation pendant les mois d'hiver, en saison sèche (Novembre, Décembre, Janvier et Février) mais maintient sa présence pendant les autres mois de l'année. *A. jeyporiensis* et *A. aconitus* présentent une fréquence saisonnière comparable à celle que manifeste *A. minimus. Toutefois,* les adultes de ces deux espèces n'ont pas été trouvés pendant la saison chaude du Nord et pendant la saison des pluies du Sud: les captures n'ont pu être réussies que d'Octobre à Avril. *A. vagus* au contraire, peu fréquent pendant les mois de Novembre, Décembre, Janvier et Mars voit son maximum de pullulation en Avril, Mai, Juin, Juillet, Août, Septembre et Octobre.

2.° — *Paludisme des zônes montagneuses.*

Ces zônes, classées dans le site 4, définies par Gourou comme régions de «hautes montagnes», sont composées de montagnes boisées avec de larges vallées et de profonds ravins. Dans ces zônes les ruisseaux abondent, constituant des cours d'eau permanents et rapides. Sol basaltique et granitique. Plateaux avec rizières étagées et à eau courante.

Elles comprennent:

— Quelques centres urbains dans le Nord, tel que Hagiang;
— De très rares plantations, des entreprises minières: Uong-bi dans le Nord, Bong-mieu dans le Centre Vietnam;
— Toutes la région des «hautes plateaux» du Centre et du Sud Vietnam.

Régions très peu peuplées, désertiques en certains endroits, seuls quelques autochtones s'accrochent dans les ravins et les vallées.

Les indices endémiques y sont très élevés:

— Indice splénique de 50 à 80 %.
— Indice plasmodique de 49 à 100 %.
— Indice gamétique de 15 à 40 %.

Les variétés, la fréquence et les variations des hématozoaires sont comparables à celles observées dans les régions de moyenne altitude: large prépondérance de *P. falciparum* pendant les mois d'hiver dans le Nord, pendant la saison pluies dans le Sud.

L'étude des espèces anophéliennes montre la grande abondance de *A. minimus* suivi par *A. jeyporiensis* et *A. maculatus*. Ont été encore identifiés: *A. aitkenii, A. barbirostris, A. gigas var. baileyi, A. hyrcanus var. sinensis, A. vagus, A. aconitus, A. fuliginosus, A. philippinensis, A. maculipalpis, A. kochi* et *A. tesselatus*.

Dans le Centre et le Sud Vietnam il faut ' ajouter: *A. maculicifacies* et *A. leucosphyrus*.

La fréquence de *A. aitkenii* et *A. kochi* est plus grande, *A. karwari* a disparu, *A. gigas, A. culifacies* et *A. leucosphyrus* ont fait leur apparition. *A. vagus* diminue de plus en plus.

Les gites de ces espèces anophéliennes sont caractérisées par:

— Ruisseaux à cours d'eau rapide, fond sablonneaux, rochers, bords herbeux;
— Emergences dans les rochers formant vasques;
— Sources alimentant des rizières étagées dans le fond des vallées.

Les espèces vectrices sont: *A. minimus, A. jeyporiensis* et *A. maculatus* auxquelles il faut ajouter *A. leucosphyrus* dans le Sud.

Les dissections des femelles adultes capturées ont donné les pourcentages d'infection naturelle ci-après:

— *A. minimus:* 3,69 %.
— *A. maculatus:* 2,42 %.
— *A. jeyporiensis:* 1,52 %.
— *A. aconitus:* 0,93 %.

La pullulation saisonnière est analoque à celle observée dans la région de moyenne altitude. A. remarquer que *A. gigas var. baileyi* a été trouvé en hiver dans les groupes de gites permanents.

3.° — *Paludisme du littoral ou Paludisme des zônes maritimes.*

Cette région, classée site 0, située en bordure de la mer, présente en certains points des côtes d'altitude très basses, parfois négatives. L'influence marine modifie assez profondément l'aspect général du pays, la nature de la flore et la faune anophèlienne. Les collections d'eau sont le plus souvent saumâtres.

Elle comprend:

— La région des lais de mer de la province de Namdinh dans le Nord;

— Les lagons de Phudien de la côte d'Annam;

— Toute la grande région des bouches du Mékong dans le sud;

— La généralité des plages du littoral Vietnamien.

Les indices endémiques montrent une grande discordance entre les indices spléniques et plasmodiques: ces derniers sont de beaucoup les plus élevés contrairement à ce que nous avons observé dans les zônes précédentes.

— Les indices spléniques: de 4 % en hiver, s'élèvent en certains endroits jusqu'à 30 et 40 % en été.

— Les indices plasmodiques: de 20 % en hiver, atteignent 60 % et plus en été. Les indices plasmodiques sont toujours et à tout âge les plus accusés.

Les trois variétés d'hématozoaires sont représentées avec, dans le jeune âge (2 à 3 ans) prépondérance de *P. vivax* (60 %), viennent ensuit avec 33 % *P. falciparum* et avec 7 % le *P. malariae*. A adolescence *P. falciparum* dépasse *P. vivax, P. malariae* restant toujours faible (15 à 17 %).

Selon Marneffe il existe dans ces régions un type de paludisme endémique faible, avec recrudescence saisonnières très fortes, de type épidémique, en Juin Juillet et Août.

La faune anophélienne est composée essentiellement par les représentants des espèces suivantes:

— *A. subpictus, A. ludlowi* var. *sundaicus* (espèces particulières à ces régions maritimes), *A. vagus, A. hyrcanus* var. *sinensis,* auxquels viennent sájouter, en nombre très restreint, *A. barbirostris, A. aconitus, A. maculipalpis* et *A. tesselatus.*

L'étude de la fréquence et des variations saisonnières des principales espèces montre:

— *Dans le Nord:*

A. vagus prépondérant pendant la saison des pluies (35 à 40 % environ), se maintient à un taux assez élevé au cours des autres périodes de l'année.

A. *hyrcanus* var. *sinensis,* très nombreux de Septembre à Mars, disparaît presque totalement en saison des pluies où il cède la place à *A. vagus.*

A. subpictus en proportion assez forte pendant toute l'année proportion qui ne descend jamais au-dessous de 20 %. et atteindre en saison des pluies jusquà 95 % des captures dans la région des lais de mer.

— *Dans le Sud:*

A. subpictus présent aussi pendant toute l'année et occupant une place importante en saison des pluies.

A. ludlowi var. *sundaicus* prépondérant pendant la saison sèche (Novembre à Mai), assez fréquent pendant les autres mois.

A. hyrcanus var. *sinensis* et *A. vagus,* de pullulation intense et constante.

Les collections d'eau saumâtre, plus ou moins riches en sel marin, ayant une végétation aquatique spéciale à ce milieu, sont les gîtes de prédilection de *A. ludlowi* var. *sundaicus* et de *A. subpictus.*

Ces deux espèces ont été trouvées infectées naturellement:

— *A. subpictus* dans le Nord, pendant la saison des pluies (0,10 %).

— *A ludlowi* var. *sundaicus* dans le Sud, pendant la saison sèche (0,15 %).

Les régions maritimes du Vitnam posent quelquefois des problèmes un peu spéciaux posés par la présence de villages, en bordure de la mer, adossés à des dunes ou à des falaises, et par certaines plages.

Dans le premier cas, l'affleurement de la couche argileuse, presque en bordure de la mer, détermine des émergences d'eau claire et courante qui sont des gîtes favorables et permanents pour *A. minimus* et *A. aconitus*. L'endémicité palustre y est fort et présente d'importantes poussées émidémiques saisonnières. Les indices spléniques dépassent 50 % et les indices plasmodiques 40 %.

Les plages, le dernier cas, se divisent en 2 catégories:

a) celles assimilables à la région deltaique, avec paludisme épidémique sur fond d'endémicité discrète, à deux poussées annuelles: Mai--Juin-Juillet et l'autre en Décembre. La faune anophélienne ne comporte pas de *A. minimus* mais seulement *A. hyrcanus var. sinensis, A. vagus, A. tesselatus* et quelques *A. subpictus* et *A. ludlowi* var. *sundaicus*. Ces deux dernières sont suspectées d'être les agents transmetteurs du paludisme de ces régions.

b) Celles dont la physiographie rappelle à la fois les sites montagneux et les régions deltaiques. Ce sont les plus nombreuses. Elles comprennent des parties basses, en général saines, environnées de rizières, de cultures sèches, etc.; et des mamelons ou collines formés de rochers dans lesquels on trouve des ruisseaux à eau claire, de petites sources, des émergences. Au pied de ces mamelons et collines existent des marais inondés à eau légèrement courante bien ensoleillés. On trouve dans ces gites la faune anophélienne pathogène des régions accidentées: *A. minimus* en grande quantité ainsi que *A. jeyporiensis* et *A. aconitus*. Les plages aménagées pour le tourisme, telle que celle de Samson dans le Nord, de Nuocngot dans le Sud et de Cuatung dans le Centre Vietnam, présentent une infection sévère:

— Indices spléniques: de 28 à 68 %.
— Indices plasmodiques: de 50 à 93 %.
— Indices gamétiques: de 18 à 62 %.

Les variations saisonnières des indices endémiques sont sensiblement semblables à celles des régions accidentées pour le Nord et le Centre Vietnam (maximum d'Octobre à Mars), pour le Sud Vietnam c'est encore pendant la saison sèche que les indices endémiques sont les plus élevés.

Les études malariologiques de ces régions ont permis de constater que:

— *Plasmodium falciparum* est l'hématozoaire le plus fréquemment rencontré, avec prépondérance de Octobre à Mars.

— *Plasmodium malariae,* rare dans le Nord et le Sud, est rencontré dans 60 % des cas dans le Centre Vietnam au début de la saison chaude (Avril-Mai).

— *Plasmodium vivax,* rare d'Octobre à Mar, se trouve à égalité avec *P. falciparum* pendant d'autre partie de l'année.

4.° — *Paludisme des deltas.*

Classée dans le site 1, la zône deltaique proprement dite, alluvionnaire récente, aux rizières basses, aux cours d'eau lents et boueux. comporte, bien que saine en général, un paludisme à caractère focal.

Cette zône comprend toute la partie rizicole du Vietnam, région très peuplée dans laquele certains lieux peu salubres ont été décelés.

Dans ces postes insalubres, au cours des poussées épidémiques de paludisme les indices:

— Splénique (en moyenne de 1 à 5 %) peut atteindre 20 %;
— Plasmodique (en moyenne de 1 à 3 %) peut atteindre 20 à 30 %;
— Gamétique (en moyenne de 0 à 2 %) peut atteindre 13 à 20 %.

L.étude des variétés des hématozoaires montre:

— La prédominance constante et marquée de *P. vivax;*
— Que *P. falciparum* ne donneque le 1/5 des infections;
— Que *P. malariae* est responsable de 10 % des cas seulement.

En période émidémique *P. falciparum* peut égaler en fréquence *P. vivax.* Il est, de plus, la cause habituelle des formes graves et mortelles (accès pernicieux, fièvres bilieuses hémoglobinuriques). Au point de vue saisonnier, l'incidence de chaque variété d'hématozoaire varie peu d'une saison à l'autre, toutefois *P. falciparum* se rencontre plus souvent au début de l'été.

Les enquêtes entomologiques ont permis d'identifier les espèces anophéliennes suivantes: *A. hyrcanus* var. *sinensis, A. vagus, A. hyrcanus* var. *nigerrimus, A. aconitus, A. barbirostris, A. tesselatus,* auxquelles viennent s'ajouter quelques rares: *A. minimus, A. subpictus, A. philippinensis* et *A. kochi.*

A. hyrcanus var. *sinensis* se trouve toujours en abondance (de 50 à 70 %) suivi de *A. vagus* (20 à 30 %).

Les dissections des femelles adultes capturées ont permis de trouver quatre espèces infectées naturellement:

— *A. hyrcanus* var. *sinensis:* de 1,50 à 2,50 %;
— *A. hyrcanus* var. *nigerrimus:* 1,40 %;
— *A. tesselatus:* 1,90 %;
— *A. vagus:* 0,50 %.

Du point de vue saisonnier, le principal responsable *A. hyrcanus var. sinensis* a son maximum de densité pendant la saison estivale, pluvieuse et chaude (Juin à Septembre).

Lesgites larvaires types sont constitués par les mares domestiques, les marécages, les bords des *suôis* et des rivières; types à eau claire, à végétation aquatique et bords herbeux. Les rizières forment des gites temporaires très importants au moment de la grosse pullulation des anophèles.

Comme de bien entendu il existe des situations exceptionnelles. C'est le cas de Phu Nhon dans le Centre Vietnam, gros village situé sur la rive gauche du *Sông Trà-Khúc*. Région purement agricole couverte de rizières, pour lesquelles les habitants ont créé un système de canaux d'irrigation alimentés par des batteries de *Norias* construites en bambous, de taille impressionnante. L'eau de la rivière est puisée par ces norias et amenéé dans les canaux d'irrigation. Phu Nhon étant un point de relâche pour les sampans venus de la Haute Région, une faune anophélienne dangeureuse est importée par leur intermédiaire et trouve des conditions favorables de reproduction dans les canaux et rigoles d'irrigation. C'est ainsi que furent capturés et idenfiés: *A. minimus, A. jeyporiensis, A. aconitus, A. vagus, A. hyrcanus* var. *sinensis, A. fuliginosus* et *A. tesselatus.*

A. minimus présente une variation saisonnière très marquée. Presque introuvable pendant la saison sèche, il pullule pendant la saison chaude et des pluies (Avril à Octobre). Les dissections des femelles capturées permirent de les trouver infectées naturellement.

Les indices spléniques, de 28 % en saison sèche, atteignant 60 % pendant la saison des pluies;

Les indices plasmodiques passent de 35 % à 85 %;

Et les indices gamétiques de 5 % à 35 %.

P. falciparum, plus fréquent en saison sèche, est en égalité avec *P. vivax* pendant la saison des pluies; *P. malariae* ayant toujours un taux assez bas.

5.° — *Paludisme de haute altitude.*

Classée dans le site 5 la zône des hautes montagnes, située au-dessus de 1 000 mètres d'altitude, avec des vallées profondes, à ruissellement abondant et cours d'eau torrentiels, est caractérisée par une flore particulière et par une faune anophélienne un peu spéciale. Elle s'identifie dans le Nord à la région de Chapa, dans le Sud au Plateau du Lang--Bian. Ces régions possèdent un paludisme autochtone rare, aux indices endémiques généralement très bas. On y observe la disparition du représentant le plus dangereux Myzomya: *A. minimus* et la présence d'une espèce nouvelle, commensale des hautes altitudes, *A. lidesayi.* Zône très peu peuplée en raison des nombreuses difficultés crées par la relief du sol, le froid et le peu de terres cultivables.

Les indices endémiques sont pratiquement négligeables:

— *Indices spléniques:* de 0 % à 3 %;
— *Indices plasmodiques:* de 0 % à 6 %;
— *Indices gamétiques:* de 0 % à 3 %.

La recherche systématique des hématozoaires a marqué la prévalence de *P. vivax* en saison chaude, montré que *P. falciparum* arrive à égaler *P. vivax* d'Octobre à Avril, et que *P. malariae* se situe toujours à un taux très bas.

Les espèces anophéliennes, à densité larvaire à peu près égale entre elle, capturées dans ces régions sont: *A. hyrcanus var. sinensis, A. gigas, A. lindesayi, A. barbirostris, A. culicifacies, A. fuliginosus* et *A. philippinensis.*

Les gites préférés des cinq espèces prédominantes sont aussi bien des creux de rochers, des ruisseaux à bords herbeux, que des terrains marécageux ou cultivés à eau légèrement courante.

L'étude de la variation saisonnière des anophèles, marque la fréquence de *A. hyrcanus var. sinensis, A. gigas, A. jeyporiensis* en hiver (saison sèche) bien plus qu'en été; indique inversement que*A. lindesayi, A. maculatus, A. culicifacies* sont plus nombreux en été (saison des pluies) qu'en hiver. Les dissections des femelles adultes capturées n'ont pas permis de trouver un anophèle infecté naturellement.

Il est possible de supposer que les facteurs météorologiques et les facteurs thermiques sont les responsables de la discordance existant entre la présence d'une faune, vectrice d'une part, et les indices malariologiques très faibles d'autre part.

6.° — *Paludisme d'importation.*

Des concours de circonstances favorables, l'usage de moyens mécaniques, etc., ont amené, en certaines régions considérées comme salubres, un paludisme dangereux.

Les mouvements de population, sous ses aspects multiples, sont une des principales causes propices à l'existence d'un paludisme élévé par la création de réservoirs de virus:

— Les mutations des soldats de l'armée vietnamienne qui, par le jeu des affectations, passent une partie de leur carrière, accompgnés de leur famille, dans les postes malsains très impaludés. Le retour de ces éléments porteurs d'hématozoaires dans une région saine peut être la cause de poussées épidémiques;

— Les ouvriers des mines ou des grandes plantations qui reviennent dans leur village natal, porteurs trop souvent d'une infection paludéenne plus intense que celle existant localement;

— Les pélerins qui, sans protection préventive, se rendent aux sanctuaires situés pour la plupart dans les régions de haute endémicité: Bimson dans le Nord, Thoson dans le Sud;

— Les estivants qui fréquentent les plages dangereuses telles que Samson, Cua, Tung, Cua Lo, Nuoc Ngot, etc.;

— Les villageois qui vont sur les marchés tenus toutes les décades en des lieux parfois très impaludés;

Sont susceptibles de devenir des éléments dangereux pour leur lieu d'origine.

Parmi les autres causes favorisants réside l'emploi des moyens mécaniques tels que: trains, barques, cars, automobiles, etc. C'est ainsi que s'est développé le paludisme des ports fluviaux dû au passage de la batellerie (exemples Hung Yen dans le Nord, Phu Nhon dans le Centre Vietnam), celui des stations d'altitude par les automobiles et les cars (routes de Chapa, de Dalat).

F) LA LUTTE ANTIPALUDIQUE AU VIETNAM.

L'aquisition de la topographie de l'endémie paludéenne, les études entomologiques (systématique, infection anophélienne) ont permis la mise en oeuvre de mesures diverses contre la propagation du paludisme.

a) Elles consistaient en *contrôle antimalarienne.*

Les enquêtes malariologiques, exécutées pendant près de 30 année par les Services Spécialisés de l'Institut Pasteur au Vietnam ont abouti à la connaissance du paludisme local. Des propositions de prophylaxie judicieuse, adapté de préférence à lutte contre les espèces anophéliennes, en furent la conclusion économique.

Le problème prophylactique consistant à rompre la chaîne palustre: Réservoir de virus → anophèle → homme sain on peut arriver à le résoudre soit:

— Par la méthode directo ou *chimioprophylaxie;*
— Par la méthode indirecte ou *antianophélienne.*

Quelle que soit la méthode: *directe* (attaque du parasite chez l'homme) ou *indirecte* (destruction des anophèles vecteurs), elle a toujours été adapté à la situation économique et sociale de la collectivité considérée car à *chaque situation palustre convient une solution particulière.*

1° — *Chimioprophylaxie.*

La prévention du paludisme avait été préconisée depuis fort longtemps par l'emploi de la quinine. Rappelons à ce sujet que le Dr. Yersin avait réussi, dès 1919, à acclimater au Vietnam l'arbre à quinquina afin de pourvoir aux besoins de ce pays en quinine.

De nombreuses expériences furent tentées pour trouver les médicaments susceptibles de permettre:

— La destruction du parasite dans sa phase pré-érythrocytique ou dans la phase asexuée érythrocytique;
— La destruction des formes éxo-érythrocytiques;
— La destruction des formes asexuées du parasite dans le sang;
— La destruction des gamètes dans le sang.

C'est ainsi, qu'avant la deuxième guerre mondiale, furent essayés avec des fortunes diverses: atébrine, plasmoquine, prémaline, quinacrine, quinio-stovarsol, quinoplasmine dans la prophylaxie des collectivités (pénitencier de Poulo-Condore, Troupes stationnées dans le Haut Tonkin, Plantations du Sud, et.). Les expériences faites au cours de la deuxième guerre mondiale permirent des gains considérables dans cette voie: sur les plantations du Sud les essais de prophylaxie collective furent entrepris, après la guerre, par l'emploi comparatif de la *paludrine* et de la *Nivaquine*[1]. Les services medicaux de ces plantations constatèrent que *P. falciparum,* responsable pour 90 % des accès palustres, devient résistant à la paludrine à partir du 13ème mois de son emploi alors que la nivaquine conserve toute son efficacité. La nivaquine fut donc adoptée en 1951 et permit de conserver les indices spléniques et plasmodiques au-dessous de 10 % chez tous les habitants vietnamiens des villages situés sur les plantations. Des expériences nouvelles furent tentées avec quelques uns des médicaments antipaludiques découverts récemment:

— Un groupe de plantations fit des essais avec *Daraprim.* Les indices spléniques et plasmodiques recherchés un mois et demi après la fin du traitement étaient en très nette régression. En plus de l'avantage d'être un des rares produits capables de détruire les formes sexuées de *P. falciparum,* un autre avantage réside dans son prix très bas: le prix de revient annuel, ramené a un individu dans la prophylaxie des collectivités, est le 1/4 de celui de la nivaquine et le 1/6 de celui de la flavoquine.

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[1] Voir *in fine* le tableau 2 donnant la liste des médicaments antipaludiques et leurs synonymes.

— D'autres groupes de plantations avaient aussi, dès 1951, adopté la nivaquine à cause des bons résultats qu'ils en avaient obtenus: régression des indices spléniques et plasmodiques aux environs de 10 %. En 1954, ils retentirent la *Flavoquine* car les manifestations toxiques de ce produit aussi actif que la nivaquine, sont particulièrement rares. En 1956, ils tentèrent quelques essais avec le «Malocide» à cause de son action supplémentaire sur la sporogonie chez l'anophèle.

D'une manière générale, à l'heure actuelle, la prophylaxie des collectivités sur les plantations consiste soit en traitements de courte durée destinés à stériliser les réservoirs de virus et en pulvérisations de D. D. T faites conjointement, soit en traitments hebdomadaires continus à raison de 3 comprimés de nivaquine par semaine et par enfant de 12 à 15 ans. Des doses réduites sont données aux enfants plus jeunes.

Dans les pays montagnards du Sud, certains villages furent choisis par les médecins de l'O. M. S. pour leurs essais de prophylaxie du paludisme par médicaments antipalustres tels que: quinacrine, chloroquine, daraprim et camoquine qui furent testés comparatitvement.

En 1949, le village de Djiring est traité à la quinacrine. Six mois après le début du traitement les indices spléniques et plasmodiques sont encore de 73,3 % et 87,3 %. La nivaquine est alors instaurée. Cinq mois de traitement font tomber les indices spléniques et plasmodiques aux environs de 20 %. En 1952, la médication fut arrêtée et l'amélioration continue à se maintenir.

Au village de Klong Trau qui avait 60 % d'indice splénique et 83 % d'indice plasmodique, la chloroquine a permis d'obtenir une réduction très rapide de ces taux et de les amener au-dessous de 10 %.

Le *Daraprim* et la *Camoquine* ont été également essayés. Les résultats obtenus permettent d'avancer que ces deux nouveaux antipaludiques constituent un progrés appréciable sur les anciens (même sur la chloroquine) car on n'observe pas, avec eux, cette remontée immédiate des indices spléniques et plasmodiques que suit, généralement, l'arrêt de distribution de médicaments antipalustres. Cependant de nouveaux essais sur la résistance doivent être entrepris avant de conclure sur la valeur de ces nouveaux médicaments.

Les médecins de l'O. M. S. ont retenu la chloroquine, plus maniable et plus efficace que la quinacrine et donnant des résultats intéressants. D'après eux, la stérilisation du réservoir de virus par des traitements de courte durée est une méthode de lutte qui conserve toute sa valeur à côté des des pulvérisations de D. D. T. dans la prophylaxie du paludisme dans les régions d'hyperendémie et d'holoendémie du Vietnam.

2.° — *Methodes antianophéliennes.*

Le problème prophylactique va être envisagé en fonction de la partie la plus vulnérable du complexe palustre: le vecteur. Cette lutte contre l'anophèle vecteur comprend soit des mesures antilarvaires, soit des mesures contre l'anophèle adulte.

a) *Mesures antilarvaires.*

L'aménagement des collections d'eau dangereuse a été fait par l'emploi soit de méthodes temporaires ou semi-permanentes, soit de méthodes permanentes:

— Les méthodes temporaires ou semi-permanentes ont été utilisées quand, pour diverses raisons, l'aménagement permanent des collections d'eau n'était pas possible pratiquement. Elles ont consisté en l'emploi de larvicides, en aménagement sommaire du terrain, en drainage à ciel ouvert, en ombrage des drains, en irrigation alternée des rizières, en emploi de poissons larvivores, etc.;

— Les méthodes permanentes ont été employées pour faire disparaître les gites permanents: pose de drains souterrains en poterie ou en ciment (collecteurs), construction d'ouvrages (barrage avec chasse d'eau, portes de marée), travaux de remblayage.

Dans le premier cas rencontrent toutes les régions agricoles à population disséminée où il a fallu traiter mares, étangs, chantiers provisoires des travaux publics (construction de ponts, routes, canaux, etc.), installations temporaires telles que charbonnières, camps de troupes en manoeuvre, etc., etc. Quelques exemples pris dans le Nord et Sud Vietnam montreront les résultats acquis.

Dans le Nord:

Sur un chantier des travaux publics ayant 40 % d'indisponibilités journalières pour paludisme, on passe, trois mois après le début des travaux antilarvaires, à 5 % d'indisponibilités.

A Tricu, les indisponibilités dépassaient 15 % de l'effectif la mortalité 10 %, les index endémiques étaient au-dessus de 40 %. Après huit mois d'emploi de larvicide (mazout) les index étaient tombés à 4 % et il n'y eut pratiquement plus de nouveaux malades par paludisme.

A la station agricole de Phuho les indices endémiques infantiles voisin de 100 % sont tombés à 30 % par le seul emploi de drains ombragés.

A Tong, camp d'aviation, où l'on notait 4 à 5 cas de primo-infection par mois, l'épandage hebdomadaire de poudre larvicide (vert de Paris) par avion a eu pour conséquence la disparition totale des cas de primo-infection et de tous cas de paludisme ensuite.

Dans le Sud:

A Phunhon toutes les larves ont disparu par le procédé, soit des irrigations alternées des rizières trois jours sur six, soit par irrigations et drainage (5 jours d'irrigation, 1 jour de drainage, 1 jour d'assèchement) sans nuire ni au rendement ni à la qualité du paddy récolté (contrôlé par l'office du riz). Le Centre de Budop exemple magnifique d'assainissement avec des moyens très limités.

*

Dans le second cas sont comprises les agglomérations dont l'importance de la population rassemblée a justifié la mise en oeuvre de procédés relativement couteux; les grandes plantations et entreprises minières où sont groupées d'importantes masses ouvrières. Partout les résultats obtenus ont montré une réduction rapide et durable du paludisme local.

Dans le Nord:

Quatre centres urbains furent choisis parmi les plus impaludés. L.un d'eux, Hagiang, surnommé *Cité de la fièvre et de la mort* avait en 1932, 70 % d'indice splénique et 81 % d'indice plasmodique. Six années plus tard, en Mars 1938, toute les formes graves du paludisme (accès pernicieux, fièvre bilieuse héglobinurique) avait disparu et les indices etaient ramenés respectivement à 4,15 % et 7,50 %. En 1944, ils étaient encore à 6 et 12 % respectivement. L'agglomération voisine, Vinh-Thuy, prise comme témoin voyait ses indices atteindre 90 % et 75 % en 1932, 62 % et 54 % en 1938, 64 % et 64,50 % en 1944. Des résultats semblables à celui de Hagiang furent enregistrés dans les trois autres centres traités, eux aussi au moyen de travaux permanents.

Dans le Sud:

Sur le grandes plantations de caoutchouc (où le taux des décès atteignit en certains points près de 100 pour mille) du fait de la mortalité par paludisme, des rapatriements et des désertions, ces exploitations pouvaient perdre en 18 mois plus de 55 % de l'effectif des travailleurs agricoles engagés. Des travaux antimalariens permanents ont permis de juguler les poussées épidémiques, de réduire considérablement le taux de la mortalité et de maintenir presque partout le taux des indisponibilités journalières au-dessous de 5 %.

b) *Mesures anti-adultes.*

Ce procédé de lutte antipalustre, dont la valeur et l'importance ont été confirmées par les rapports de Congrès, Conferences et Comités d'experts du paludisme, a été employé un certain temps (1929/1930) dans les habitations de l'Indochine méridionale. Ce procédé était surtout actif à la fin de la saison des pluies et au début de la saison sèche (Novembre à Mars compris). Les moyens dont on disposait à cette époque ne permettaient pas la destruction des anophèles adultes dans les grands centres urbains. La méthode la plus simple résidait dans l'éloignement des gites par le nettoyage, le débroussaillement des environs des habitations, l'entretien dans un rayon de 300 mètres d'une surface de terre nue ou d'un gazon régulièrement fauché tous les 15 jours.

Actuellement les principaux procédés préconisés pour la desinsectisation sont: les captures par pièges et manuelles, la protection mécanique, les procédés chimiques.

Captures par pièges et manuelles.

Ces procédés ne sauraient jamais être envisagés comme moyen de lutte et d'assainissement. Ils permettent seulement de connaître la variété de la faune anophélienne et son importance, ce qui peut amener des modifications dans la prophylaxie mise en oeuvre.

Protection mécanique.

Les procédé de protection mécanique: moustiquaires, maisons grillagées, ne peuvent être compris comme moyens de lutte d'ensemble. L'utilisation de la moustiquaire tendait, en 1939, à se généraliser dans toutes les masses populaires du Vietnam. Cette barrière entre l'anophèle et l'homme est afficace à condition que les usagers ne transforment ce moyen de protection en piège à moustiques.

Procédés chimiques.

Au début de la lutte contre le paludisme la destruction des anophèles adultes par les vapeurs de crésyl (procédé de Bouet et Roubaud) a été un adjuvant précieux de la lutte antilarvaire dans les situations où les maisons à traiter étaient peu nombreuses. En général, cette méthode est onéreuse et inefficace à elle seule pour protéger une collectivité ouvrière ou des centres urbains en région d'endémie palustre élevée.

Depuis la découverte des insecticides à effet rémanent, la destruction des insectes adultes tend au contraire à prendre la première place dans les mesures semi-temporaires de prophylaxie anti-anophélienne.

L'efficacité d'une pulvérisation bien faite, avec les produits de bonne qualité, a une durée minimum de trois mois. Cette méthode est actuellement préconisée par les meilleurs malariologistes et doit rendre de très grands services en Indochine.

Dans les pays montagnards du Sud Vietnam, M. E. Farinaud et Chou Mara firent plusieurs essais de prophylaxie du paludisme par pulvérisation de D. D. T. Les résultats obtenus sont très encourageants et confirment amplement ceux observés dans les pays voisins du Vietnam.

Commencées en 1948, ces expériences donnent des résultats spectaculaires: au canton de Yang-Lak, comprenant 2 650 habitants, l'indice splénique qui était au départ de 73,4 % est descendu à 15,3 % en Février 1953, l'indice plasmodique de 50,7 % à 3,1 %, l'indice gamétique de 7,9 % à 0,7 %. L'indice plasmodique des nourrissons (0 à 1 an) qui était de 46,7 % en 1950 est tombé à 0 % en 1952 et s'y est maintenu à ce taux en 1953. Ces résultats ont été obtenus après sept pulvérisations de D. D. T., échelonnées sur quatre années.

La régression de l'indice splénique paraît s'effectuer beaucoup plus vite dans les villages à population strictement vietnamienne que chez ceux à population montagnarde. Ainsi dans le village de Phuonghoa (521 habitants vietnamiens) l'indice splénique, qui était de 81,2 % en Novembre 1949, descend à 11,2 % en Mars 1952 et se stabilise à 5 % ensuite. Dans un autre village, Phuong-Nghia, (1 334 habitants vietnamiens) l'indice splénique passe de 53,5 % en Novembre 1948 à 14 % en Juin 1950 et à 1,6 % en Décembre 1952. Environ deux années seulement ont été nécessaire pour ramener l'indice splénique aux alentours de 10 %. Comparativement, dans les villages à population montagnarde, après le même temps d'observation l'indice splénique est encore aux environs de 30 %.

D'autre part, la lutte antipaludique entreprise par les services médicaux des plantations de caoutchouc du Sud Vietnam comprend également, depuis 1946, la destruction des anophèles adultes au moyen d'insecticides à effet rémanent. Des résultats remarquables on été signalés:

— Sur la plantation de X..., les indices spléniques qui étaient en 1949 de 75 % et 84 % ont été ramenés à 12 et 14 % en 1951;

— Sur la plantation Y..., les indices spléniques de 28 % et 24 % en 1949 ont été réduits à 2,7 % en 1951;

— Les plantations de M... accusaient en 1930, chez les Vietnamiens, un indice splénique de 60 et 100 %, un indice plasmodique de 25 et 100 %. En 1948, début des pulvérisations de D. D. T. En 1954, les indices étaient respectivement de 4,8 % et de 0 %. Même résultats chez la population malaise de la plantation: en 1948 indice splénique de 100 % et indice plasmodique de 100 %, en 1954 les indices étaient réduits à 8,8 % et 1,8 %;

— Aux plantations de L..., en 1943, les taux ci-après avaient été relevés: indice splénique = 60 à 94 %, indice plasmodique = 30 à 94 %, indice gamétique = 16 à 32 %. Dans un village témoin, hors plantation, l'indice splénique = 100 % et l'indice plasmodique = 83 %. En 1956, dans les villages situés sur les plantations les taux on été ramenés de 7 à 18 % d'indice splénique, 2,7 % d'indice plasmodique, 0,3 % d'indice gamétique, alors que ceux du village témoin restent à 75 % d'indice splénique, 83 % d'indice plasmodique et 38 % d'indice gamétique.

Plus récemment, le Bureau du contrôle malariologique du Ministère de la Santé Publique du Vietnam a oeuvré énormement avec l'aide de l'U. S. O. M. pour l'installation d'un million de refugiés venant du Nord et l'exécution du plan de développement des fermes de peuplement dans l'arrière pays, au-dessous du 17è parallèle.

Une centaine de localités à haute endémicité palustre, ont été choisies, défrichées, rendues saines par les pulvérisations systématiques de D. D. T. La population ont pu s'y implanter aisément, se développer et s'accroître. Ces localités ne tarderont par dans un avenir proche à s'élargir en tâche d'huile, à se joindre transformant des zônes jusqu'ici presque désertiques en régions fertiles et nourricières.

Ces résultats montrent, tant dans la zône d'expérience des pays montagnards que sur les plantations de caoutchouc du Sud Vietnam ou les fermes de peuplements, que les pulvérisations de D. D. T., bien conduite, ont provoqué la disparation presque complète du paludisme en tant que maladie sociale.

c) *Eradication du paludisme.*

De nous jours, nombre de pays dans le monde ont réussi à faire disparaître complètement le paludisme grâce à la pulvérisation d'insecticides à effet rémanent et à la chimiothérapie combinées.

Aussi notre pays s'y engage fermement dans cette voie. Par decret Présidentiel signé le 6/2/1958 un Service National de l'Eradication du Paludisme a été institué.

Ce service, aidé par l'U. S. O. M., est en voie d'organisation et un programme d'action a été dressé pour une durée de 5 ans.

Nous espérons qu'à la fin de cette année 1958 nous pourrons entrer dans la phase opérationnelle.

G) INFLUENCE DES MESURES ANTIPALUSTRES SUR LA SITUATION ECONOMIQUE.

La première conséquence de la disparition du paludisme, a été de fixer les populations dans les régions anciennement impaludées, de permettre aux enfants nés dans ces régions de vivre et de se développer jusqu'à l'âge adulte, à l'abri du paludisme.

Le rendement supérieur de la main d'oeuvre a favorisé, plus tard, l'établissement de plus de 3 000 exploitations agricoles en Indochine méridionale et de 800 concessions domaniales pour le Centre et le Nord Vietnam.

La culture du caoutchouc seule, en 1943, occupait 1 085 plantations ayant 138 954 hectares de superficie plantée contre 9 000 en 1919. La production du caoutchouc est passée de 340 tonnes en 1900 à 74 793 tonnes en 1943.

La production du charbon de bois dans le Sud Vietnam qui était de 50 000 tonnes en 1931, atteignait 92 000 tonnes en 1940. Les plantations de café, thé, cannes à sucre, etc., etc, se sont développées dans les mêmes proportions.

Les régions minières, si touchées par l'endémie palustre, ont après la mise en place de travaux antimalariens, atteint un essor considérable. La production du charbon est passée de 20 000 tonnes en 1900 à 2 500 00 tonnes en 1940; celle de l'étain de 2 tonnes en 1903 à 1 499 tonnes en 1940; celle du zinc de 800 tonnes en 1906 à 6 880 tonnes en 1940 et celle du fer de 5 800 tonnes en 1919 à 140 700 tonnes em 1939; pour ne citer que les plus importantes.

Les autres enquêtes menées par l'Institut Pasteur au Vietnam ont permis:

— D'amenager les charbonnières du Sud Vietnam dans les régions de Trian, Chon Thanh, Camau, etc., etc.;

— D'établir la petite colonisation des vietnamiens du Nord dans les régions précédemment insalubres du Centre et du Sud (région de Triton par exemple);

— De développer les fermes de colonisation choisies comme modèle dans les trois grandes régions du Vietnam;

— De faire deux récoltes annuelles de paddy, par construction de travaux d'hydraulique agricole, dans les lieux où l'on arrivait péniblement, à en faire une (do Luong, Yen Khanh, etc.);

— De percer et de construire, soit des routes débloquant tout l'arrière pays (route n.° 13, n.° 20, etc.), soit des lignes de chemin de fer.

L'amélioration des conditions d'existence qui en est résultée a entraîné des progrès dans l'hygiène de l'alimentation, de l'habitation, du vêtement, progrès qui ont eu leur incidence sur la morbidité par paludisme comme sur la morbidité générale.

Les conséquence de la lutte antimalarienne menée au Vietnam peuvent être résumées comme il suit:

a) *Pour les travailleurs:*

— Réduction du nombre des indisponibilités personnelles;
— Meilleur rendement au travail;
— Diminution de la morbidité et de la mortalité générale;
— Amélioration notable de leur mode d'existence.

b) *Pour les familles:*

— Augmentation de la natalité;
— Diminution de la mortalité infantile.

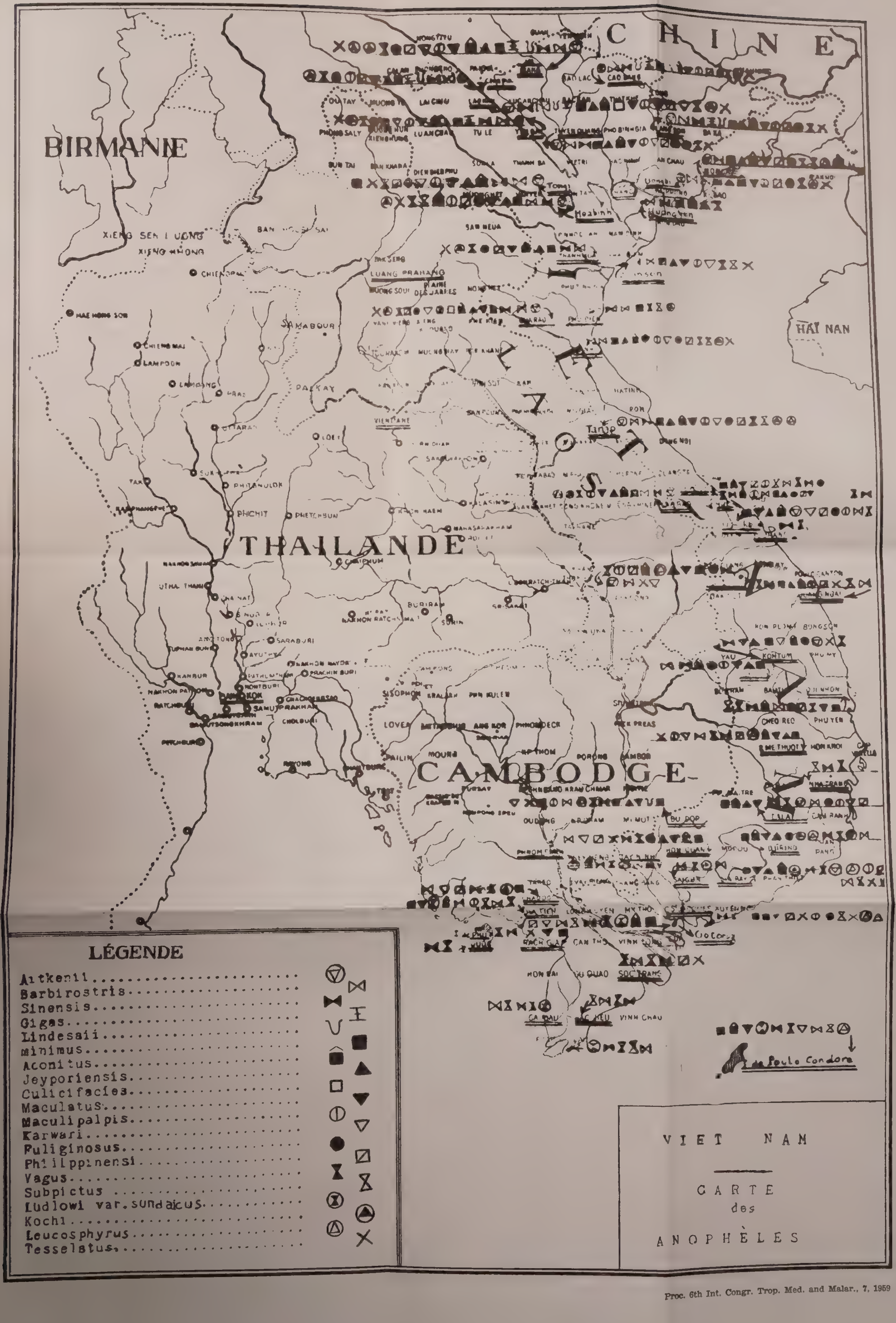
c) *Pour le pays:*

— Mise en valeur de l'arière du pays;

— Accroissement sans cesse accru de la production amenant richesse et prospérité.

CONCLUSION

Cette étude nous montre la complexité du problème du paludisme au Vietnam, nous avons ralaté ce qui avait été fait et les progrès de la lutte anti-paludisme en ce pays. Nous espérons qu'avec persévérance et discipline, nous pouvons obtenir le succès définitif avec notre programme de l'éradication du paludisme.


CHINE
BIRMANIE
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VIET NAM
HAÏ NAN
LUANG PRABANG
VIENTIANE
PLAINE DES JARRES
CHIENG MAI
LAMPOON
LAMPANG
PHITSANULOK
PHICHIT
SARABURI
AYUTTHAYA
BANGKOK
CHOLBURI
ANGKOR
PHNOMPENH
KONTUM
BAN ME THUOT
SAIGON
CA MAU
SOC TRANG
MY THO
CAN THO
RACH GIA
HOABINH
HUNGYEN
CAO BANG
LAI CHAU
PHONG SALY
SON LA
SAM NEUA
BA RIA
Ile de Poulo Condore
LÉGENDE
Aitkenii
Barbirostris
Sinensis
Gigas
Lindesaii
minimus
Aconitus
Jeyporiensis
Culicifacies
Maculatus
Maculipalpis
Karwari
Fuliginosus
Philippinensi
Vagus
Subpictus
Ludlowi var. sundaicus
Kochi
Leucosphyrus
Tesselatus
VIET NAM
CARTE des ANOPHÈLES

CHIMIOPROPHYLAXIE

MEDICAMENTS ANTIPALUDIQUES ET LEURS PRINCIPAUX SYNONYMES

AMODIAQUINE

Cam-aqui
Camoquine
Flavoquine
Miaquine
SN 10751

CHLOROQUINE

Aralen
Avloclor
Nivaquine
Rosochine
Tanakan
SN 7618
3377 RP

MEPACRINE

Acrichim
Acriquine
Atebrine
Quinacrine
Malaricida
Palusan
Methoquine
Erion
Haffkinine
Italchina

PAMAQUINE

Aminoquin
Beprochin
Pamaquine
Plasmoquine
Praequine
Rhodoquine
Plasmocide
Quipenyl
Gamefar
Fourneau 710

PROGUANIL

Bigumal
Chlorguanide
Chloriguane
Diguanyl
Paludrine
Palusil
Tirian
3359 RP
SN 12837
M 4888

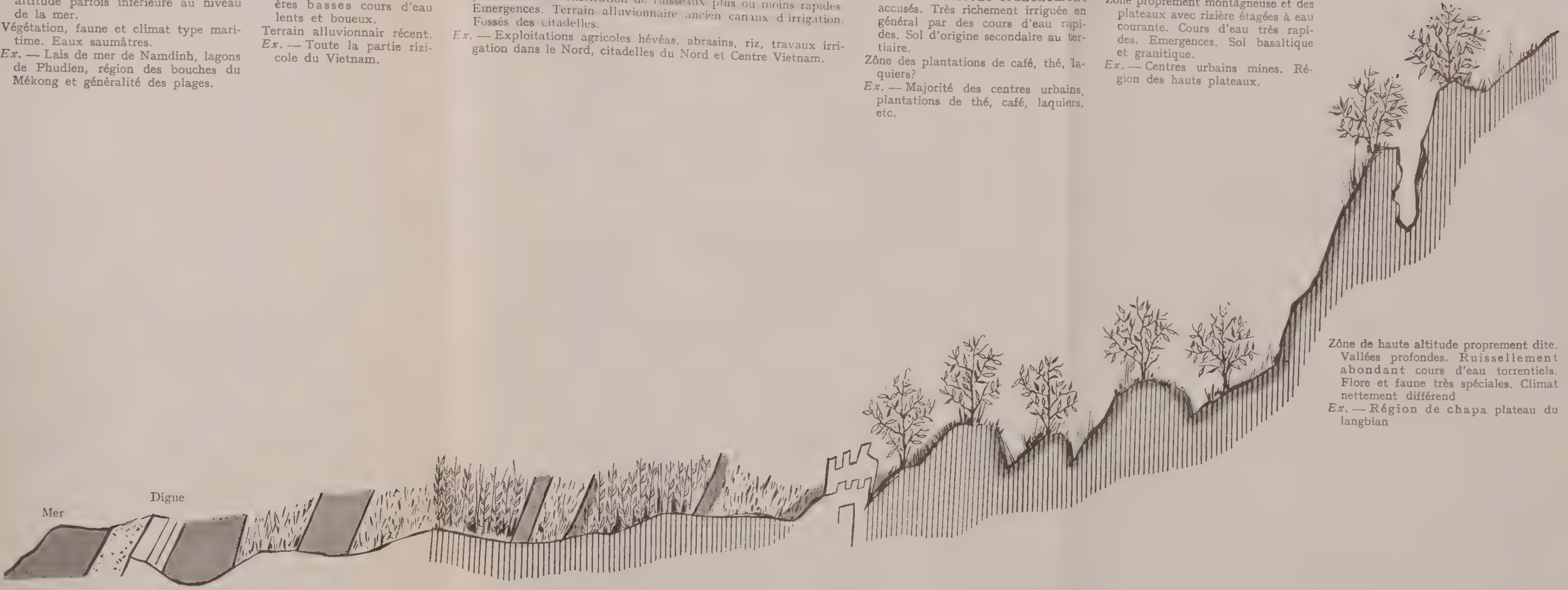
PYRIMETHAMINE

B. W. 50-63
Daraprim
Malocide

PRIMAQUINE

SN 13272

Site 5	au dessus de 1.000 m
Site 4	de 300 m à 1.000 m
Site 3	de 20 m à 300 m
Site 2	de 10 m à 20 m
Site 1	Im
Site 0	cote 0



	Site 0	*Site 1*	*Site 2*	*Site 3*	*Site 4*	*Site 5*
	Région maritime basse ou littorale. Plages, lais de mer, palétuviers. Cote altitude parfois inférieure au niveau de la mer. Végétation, faune et climat type maritime. Eaux saumâtres. *Ex.* — Lais de mer de Namdinh, lagons de Phudien, région des bouches du Mékong et généralité des plages.	Zône deltaique proprement dite. Eeaux douces. Rizières basses cours d'eau lents et boueux. Terrain alluvionnair récent. *Ex.* — Toute la partie rizicole du Vietnam.	Zône intermédiaire dite des «tertasses». Les accidents de terrain permettent la constitution de ruisseaux plus ou moins rapides Emergences. Terrain alluvionnaire ancien canaux d irrigation. Fossés des citadelles. *Ex.* — Exploitations agricoles hévéas, abrasins, riz, travaux irrigation dans le Nord, citadelles du Nord et Centre Vietnam.	Zône de mamelons franchement accusés. Très richement irriguée en général par des cours d'eau rapides. Sol d'origine secondaire au tertiaire. Zône des plantations de café, thé, laquiers? *Ex.* — Majorité des centres urbains, plantations de thé, café, laquiers, etc.	Zône proprement montagneuse et des plateaux avec rizière étagées à eau courante. Cours d'eau très rapides. Emergences. Sol basaltique et granitique. *Ex.* — Centres urbains mines. Région des hauts plateaux.	Zône de haute altitude proprement dite. Vallées profondes. Ruissellement abondant cours d'eau torrentiels. Flore et faune très spéciales. Climat nettement différend *Ex.* — Région de chapa plateau du langbian
Especes anopheliennes % vecteurs % fréquence	*A. subpictus* 20 % *A. ludlowi* v. *sundaicus* 20 % *A. sinensis* 45 % *A. vagus* 25 % *A. aconitus* *A. tessellatus* *A. barbirostris* *A. maculipalpis* } 10 %	*A. sinensis* 52 % *A. vagus* 43 % *A. nigerrimus* 3 % *A. nigerrimus* *A. aconitus* } 3 % *A. barbirostris* *A. tessellatus* } 2 % *A. philippinensis* *A. kochi* *A. subpictus* *A. minimus* } Rares	*A. minimus* 25 % *A. aconitus* 5 % *A. vagus* 15 % *A. sinensis* 40 % *A. barbirostris* 10 % *A. fuliginosus* 3 % *A. maculipalpis* *A. philippinensis* *A. tessellatus* *A. kochi* } 2 %	*A. minimus* 20,7 % *A. jeyporiensis* 10 % *A. aconitus* 5 % *A. sinensis* 32,4 % *A. vagus* 16,9 % *A. maculatus* 4 % *A. aitkénii* *A. barbirostris* *A. fuliginosus* *A. kawari* *A. maculipalpis* *A. philippinensis* *A. kochi* *A. tessellatus* } 11 %	*A. minimus* 36 % *A. maculatus* 10 % *A. jeyporiensis* 10 % *A. aconitus* 2 % *A. sinensis* 25 % *A. vagus* 5 % *A. aitkénii* *A. gigas* *A. barbirostris* *A. culicifacies* *A. fuliginosus* *A. maculipalpis* *A. philippinensis* *A. kochi* *A. leucosphyrus* *A. tessellatus* *A. culicifacies* } 7 %	*A. jeyporiensis* 15 % *A. gigas* 20 % *A. lindesayi* 20 % *A. maculatus* 20 % *A. sinensis* 10 % *A. aitkénii* *A. barbirostris* *A. culicifacie* } 3 % *A. vagus* 1 % *A. fuliginosus* *A. philippinensis* *A. kochi* } 1 %
% d'infection naturelle	*A. subpictus* 0,10 % *A. ludlowi* v. *sundaicus* 0,15 %	*A. sinensis* 1,50 % à 2,50 % *A. nigerrimus* 1,40 % *A. tessellatus* 1,90 % *A. vagus* 0,50 % Epidémies de 1934 et 1936 *A. sinensis* 4 et 5 %	*A. minimus* 1,56 % *A. aconitus* 0,01 % *A. vagus* 0,02 %	*A. minimus* 3,69 % *A. jeyporiensis* 1,00 % *A. aconitus* 0,65 %	*A. minimus* 3,69 % *A. maculatus* 2,42 % *A. jeyporiensis* 1,52 % *A. aconitus* 0,93 %	NEANT
Indices endémiques	Hiver / Eté	Poussées / Epidémies				
Indice splémique	4 % / 30 à 40 %	1 à 5 % / 20 %	10 à 20 %	35 à 50 %	50 à 80 %	0 à 3 %
» plasmodique	20 % / 60 %	1 à 3 % / 20 à 30 %	10 à 15 %	15 à 45 %	49 à 100 %	0 à 6 %
» gamétique		0 à 2 % / 13 à 20 %	5 à 8 %	5 à 11 %	19 à 40 %	0 à 3 %
Hématozoaires Fréquence et variations	Jeune âge: *P. Vivax* ÷÷÷÷ *P. falciparum* ÷÷ *P. malariae* rare Adolescence: *P. vivax* *P. falciparum* *P. malariae* rare	*P. vivax* 60 à 70 % *P. falciparum* 20 % *P. malariae* 10 % Epidémies: *P. vivax* *P. falciparum*	Sud: *P. falciparum* — Prépondérant saison des pluies *P. vivax* — Prépondérant saison sèche *P. malariae* — Rare tout l'année Nord: *P. falciparum* — Prépondérant saison sèche (hiver) *P. vivax* — Prépondérant saison des pluies (été) *P. malariae* — Rare toute l'année	Sud: *P. falciparum* ÷÷÷÷ en saison des pluies *P. vivax* — Taux stationnaire Nord: *P. falciparum* ÷÷÷÷ en hiver *P. vivax* — Taux stationnaire Adolescence: *P. vivax* — *P. malariae*	Sud: *P. falciparum* ÷÷÷÷ en saison des pluies et croissant avec l'âge *P. vivax* ÷÷ et décroissant avec l'âge Nord: *P. falciparum* ÷÷÷÷ en hiver croissant avec l'âge *P. vivax* ÷÷ décroissant avec l'âge *P. malariae*, *P. vivax*, très rapidement paludisme hyperendémique	*P. vivax* ÷÷÷÷ *P. falciparum* ÷÷ *P. malariae* ÷ En hiver: *P. vivax*, *P. falciparum*
Exceptions:	Paludisme des plages Epidémies saisonnières	Paludisme des Norias Paludisme pratiquement Paludisme focal	Paludisme des citadelles. Paludisme endémique. Zône non atteinte sévèrement. Peut disparaitre devant mise en valeur du sol.	Paludisme hyperendémique presque permanent. Pas de colonisation vietnamienne spontanée		Pas de Paludisme permanent. Influence climatique et thermostatique

L'ANOPHELISME EN ITALIE APRES DIX ANNEES DE PULVERISATIONS AVEC D. D. T.

G. Raffaele

L'éradication du paludisme en Italie, heureux résultat des pulvérisations avec le D. D. T., a été suivie par des modifications de la faune anophélienne dans les endroits traités et par des changements des habitudes des anophèles.

Parmi les espèces d'anophèles qui se trouvent en Italie, celles qui présentent le plus d'intérêt sont naturellement les espèces endophiles et endophages, surtout celles qui jouaient un rôle dans la transmission du paludisme.

Avant les pulvérisations avec le D. D. T., les anophèles vecteurs du paludisme étaient *A. labranchiae* et *A. sacharovi*. Dans les régions méridionales il y avait aussi *A. superpictus*. *A. sacharovi* était particulièrement nombreux le long du littoral adriatique. A coté de ces espèces endophiles et endophages il y en avait d'autres, comme *A. maculipennis maculipennis*, *A. messeae* et la var. *atroparvus*, qui ne jouaient pas un rôle important dans la transmission, quoique ils étaient aussi endophiles, mais, étant zoophiles, ils préféraient piquer les animaux et s'abritaient à préférence dans les étables.

Après les pulvérisations avec D. D. T., les anophèles disparurent presque immédiatement de toute pièce habitée, soit dans les chambres d'habitation soit dans les étables. Ils disparurent si vite de tout milieu domestique qu'on se demandait s'il était possible qu'en si peu de temps le D. D. T. avait pu tuer l'innombrable population anophélienne présente. Mais quand on laissait quelques étables sans pulvérisation on y capturait grand nombre d'anophèles, tandis que dans les étables traitées, même quand elles étaient très proches de celle de control, on n'en capturait que très rarement.

Dans la province de Frosinone, où nous avons conduit nos recherches sur le comportement de l'anophélisme après les pulvérisations, nous avons comparé les captures d'anophèles dans les étables de contrôle laissées sans pulvérisations, avec celles qu'on faisait en 102 étables traitées. Comme on peut juger par le graphique annexe, la différence était considérable. Avant les pulvérisations on avait établi que les espèces d'anophèles présentes dans les zones paludiques étaient surtout du groupe *maculipennis*. *A. labranchiae* en représentait le 30-50 pour cent; des autre espèces, *A. maculipennis maculipennis* était la plus fréquente. Il y avait aussi en abondance, comme partout en Italie, *A. claviger*, et dans quelques zones on trouvait aussi *A. superpictus*. Bientôt après les pulvérisations avec D. D. T. nous n'avons plus trouvé ni larves ni adultes d'*A. superpictus*, qui avait en effet une distribution très limitée, mais on trouvait presque partout grand nombre de larves d'*A. maculi-*

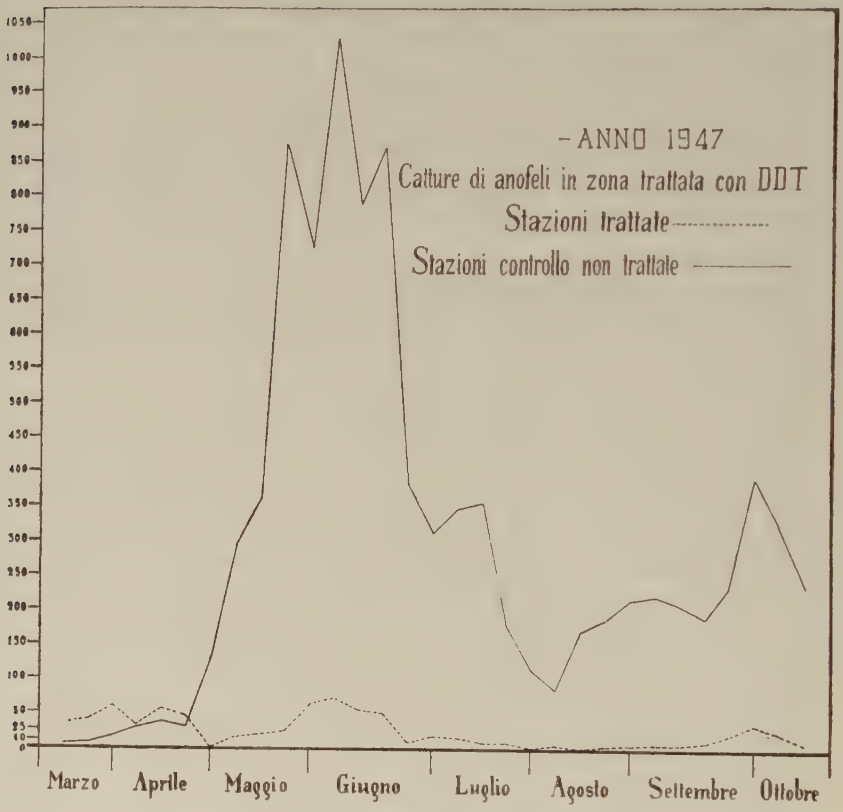


Grafico I.

pennis. L'examen de l'ovodéposition des femelles de cette espèce capturées dans les étables de contrôle non pulvérisées nous montra qu'il s'agissait de *A. maculipennis maculipennis* et parfois de *A. messeae* ou de *A. melanoon*; mais depuis 1949 jusqu'à présent nous n'avons plus trouvé aucun spécimen d'*A. labranchiae*, qui était nombreux avant les pulvérisations qui ont été commencé en 1947. En deux années le vecteur avait disparu, ce qui nous frappa surtout en considérant l'abondance du *maculipennis* typique qui, quoique zoophile, était autant endophile que le *labranchiae* et aurait dû ressentir à peu près le même effet des pulvérisations que l'on faisait aussi dans les étables.

Puisque le Haut Commissariat pour l'Hygiène et la Santé Publique avait confié à l'Institut de Malariologie de Rome la charge de surveiller l'anophélisme de plusieures zones où l'on avait fait des pulvérisations avec D. D. T., nous eûmes la possibilité de faire des recherches comparatives sur l'anophélisme des différentes régions jadis malariques et maintenant assainies par les pulvérisations. Nous avons observé que l'effet radical du D. D. T. sur *A. labranchiae*, constaté à Frosinone et, ensuite, dans certaines régions du littoral de la mer tyrrhénienne, ne s'observait pas dans d'autres régions; surtout le long du littoral adriatique parfois on trouvait en abondance *A. labrancriae* et *A. sacharovi*.

Dans la province de Frosinone les pulvérisations ont été interrompues en 1951. Depuis 1949 jusqu'à aujourd'hui nous avons examiné 53 341 ovodépositions du groupe *maculipennis* sans trouver d'*A. labranchiae*.

Aussi dans l'île d'Elbe il y avait des zones où la présence d'*A. labranchiae* avait causé plusieurs épisodes épidémiques de paludisme; le dernier, particulièrement important, se vérifia après la fin de la seconde guerre mondiale et fut étudié par Buonamini et col. (1948), qui en juin 1947 firent exécuter des pulvérisations de D. D. T. dans toutes les maisons des zones paludéennes, où l'on ne trouvait que *A. labranchiae*. Ici, comme partout, les anophèles disparurent rapidement de toute pièce pulvérisée, mais on en capturait encore plusieurs dans 3 porcheries qu'on n'avait pas pulvérisées pour contrôler l'effet du D. D. T.; les larves persistaient nombreuses et elles ne disparurent qu'après des irrorations périodiques de pétrole et de vert de Paris des gîtes larvaires. Les pulvérisations et les irrorations antilarvaires furent répétées en 1948, mais déjà les anophèles étaient devenus très rares. Après le second traitement la transmission fut interrompue et après le troisième traitement en 1949 on cessa toute intervention antianophélique. *A. labranchiae* n'a plus été trouvé après. Des recherches minutieuses en 1956 et 1957, six ans après l'interruption de toute lutte antianophélique, confirmèrent l'éradication de *A. labranchiae* de l'île.

Cependant l'expérience de l'Elbe a montré que les pulvérisations à elles seules n'auraient pas été suffisantes pour l'éradication de l'espèce. D'après Buonomini et Coluzzi (1958) l'association de la lutte antilarvaire a été le facteur déterminant de la réussite de l'éradication. Même en Sardaigne, où l'Erlaas a exécuté le plus colossal tentatif d'éradication des vecteurs que l'on connaisse, l'éradication de *A. labranchiae* n'a pas été atteinte avec les seules pulvérisations; il a fallu associer la lutte antilarvaire aux pulvérisations, car on s'aperçu vite que celles-ci n'étaient pas suffisantes à atteindre le but.

Il est donc difficile d'expliquer comment dans certaines zones de l'Italie continentale *A. labranchiae* ait disparu si facilement après 2-3 années de simples pulvérisations avec D. D. T. des habitations et des étables. Il y a, il est vrai, des zones, comme, par exemple, celle du littoral en province de Caserta, entre le fleuve Garigliano et le lac de Patria, où Buonomini (1940) avait établi la présence de toutes les espèces du groupe *maculipennis* (exceptée la var. *atroparvus*) avec prédominance de *A. labranchiae* et *A. sacharovi*. Des recherches répétées et très minutieuses exécutées par A. Coluzzi entre 1955 et 1957 ont été tout a fait négatives; il n'a jamais capturé ni adultes ni larves de toute espèce d'anophèles. Les travaux d'assainissement, les pulvérisations des maisons et les irrorations avec D. D. T. des gîtes larvaires exécutées en 1943-44 par les armées alliées, même à l'aide d'avions, et l'énorme nombre de *Gambusiae* présent dans toutes les collections d'eau, ont fait disparaître les anophèles.

Buonomini et Coluzzi (1958), en considérant les résultats qu'on a eu en Italie avec le D. D. T., expriment l'opinion que les pulvérisations en elles mêmes peuvent interrompre la transmission et éradiquer le paludisme, mais ne parviennent pas à causer une réduction évidente des anophèles. En effet nos recherches dans toutes les zones jadis malariques, nous amènent à la conclusion que l'éradication du paludisme est moins le résultat de la destruction des anophèles effectuées par le D. D. T. que la conséquence de leur éloignement des milieux habités. La possibilité de piquer fréquemment l'homme, condition essentielle pour assurer la transmission, est entravée par la présence de l'insecticide sur les surfaces des chambres habitées et des étables. Les moustiques, aussitôt qu'ils prennent contact avec les parois pulvérisées, sont poussés par l'action de l'insecticide à s'en éloigner aussi vite que possible. Coluzzi a pu le constater en suivant les mouvements des anophèles dans les étables pulvérisées au tomber de la nuit. Le contact avec les parois est trop bref pour causer une mortalité élevée, puisque même après une heure de contact forcé avec une surface pulvérisée, comme il arrive dans les tubes apprétés selon la méthode de Busvine e Nash, plusieurs anophèles survivent. Il est donc peu vraisemblable qu'un bref contact puisse en tuer un grand nombre jusque à produire l'éradication de l'espèce.

L'éradication de *A. labranchiae* qu'on a observée dans certaines zones d'Italie peu de temps après les pulvérisations de D. D. T. ne peut pas être dûe à l'action toxique de l'insecticide, d'autant plus que dans d'autre régions, telles que la Pouille, la Sicile, la Sardaigne, où l'on a fait des pulvérisations chaque année depuis dix ans, *A. labranchiae* persiste souvent en grande nombre et parfois on y trouve nombreux aussi *A. sacharovi*. Le paludisme de ces régions, jadis endémique et grave, a disparu, ce qui montre que la persistance des vecteurs a peu d'importance quand ils ne trouvent plus convenable de s'abriter dans les milieux domestiques. Peut être que dans certaines zones les maisons et les étables représentent une condition essentielle de vie pour *A. labranchiae*, tandis que dans d'autres zones il a trouvé la possibilité de vivre hors des habitations. Dans la province de Frosinone, où *A. labranchiae* a disparu très rapidement, *A. maculipennis maculipennis*, endophile comme le premier, a persisté, parce que, évidemment, il a trouvé la possibilité de vivre à l'extérieur des maisons.

Nous avons pensé aussi à la possibilité d'une différence de resistance aux insecticides des vecteurs dans les différentes régions, mais des études et des recherches minutieuses rendent peu vraisemblable cette possibilité.

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OBSERVATIONS SUR LE DEGRÉ DE RÉSISTANCE AU D. D. T. DES ANOPHÈLES ITALIENS

G. Raffaele

Nous avons commencé à nous occuper en Italie du problème de la résistance des anophèles au D. D. T. rélativement tard, quand déjà on avait accompli plusieures études à cet égard. Nous étions en effet à peu près sûrs qu'aucune résistance au D. D. T. ne s'était produite en Italie, opinion qui était partagée par tous ceux qui avaient suivi les effets des pulvérisations. Cependant, comme dans la majorité des zones pulvérisées on trouvait plusieures larves d'anophèles et aussi des adultes dans les pièces non pulvérisées, nous nous sommes posé la question si la persistance d'un nombre élevé d'anophèles pouvait être en rapport avec la production d'un certain degré de resistance. En effet on ne trouvait pas d'anophèles dans les pièces pulvérisées, mais je pensais que cela pouvait être dû au fait qu'ils n'avaient pas encore atteint un degré de resistance qui leur eût permis de rester sur les surfaces pulvérisées sans ressentir les effets du toxique, comme Livadas avait observé en Grèce (1951).

Cette opinion était fondée sur la constatation que *Anophèles labranchiae* et *A. sacharovi* persistaient dans certaines zones d'Italie, tandis que ils avaient disparu dans d'autres.

Pour capturer un nombre d'anophèles suffisant à en essayer la sensibilité au D. D. T. nous avons rencontré quelques difficultés, car dans les zones pulvérisées on n'en trouvait pas ni dans les maisons ni dans les étables. Il fallut parfois faire recours à des pièges avec un animal, mais en général il était possible d'en capturer plusieurs en les cherchant dans leurs abris hors des habitations.

Pour l'essai de la sensibilité nous avons appliqué la methode de Busvine et Nash, mais nous avons tâché d'éliminer toute cause de mortalité en dehors de l'action toxique du D. D. T., c'est à dire: 1 — nous avons capturé chaque anophèle dans un tube à part, en éliminant la capture par aspiration de plusieurs moustiques dans le même tube, car

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elle est cause de traumatismes et de mortalité. Un moustique traumatisé peut avois une sensibilité au toxique différente d'un moustique normal; 2 — chaque moustique a été exposé séparément au contact pendant une heure avec la surface irrorée avec D. D. T.; 3 — après la période de contact on passait chaque moustique séparément dans un tube avec papier filtre humide, comme pour l'ovodéposition. Nous avions l'expérience que les moustiques introduits séparément dans les tubes à ovodéposition y survivent jusqu'à 72 heures, souvent en proportion du 100 pour cent. Dans ces tubes l'humidité rélative représentait un optimum. Pour assayer la sensibilité au D. D. T. on choisissait exclusivement les femelles gorgées de sang et avec des oeufs en voie de maturation.

Les détails des expériences exécutées pendant les années 1956-1957, ainsi que les résultats obténus, ont été exposés dans des notes publiées en 1956, 1957 par moi en collaboration avec M. Coluzzi. Ce dernier a accompli aussi des recherches en Somalie (1958) sur la sensibilité au D. D. T. d'*A. gambiae, A. funestus, A. coustani* et *A. pharoensis*.

En comparant les résultats que nous avons eu en appliquant la méthode «standard» de Busvine et Nash avec ceux observés en modifiant cette technique, nous avons pu constater que la mortalité que l'on observe avec la méthode «standard» est dûe pour un pourcentage élevé, environ 75 %, aux traumatismes causés par l'aspiration de plusieurs moustiques dans le même tube et par l'exposition au contact dans des tubes d'essai de 5-6 ou plus moustiques en même temps. Nous avons constaté qu'il n'y a pas de différence de mortalité en introduisant dans le tube de contact 1 ou 2 moustiques, mais en augmentant leur nombre la mortalité devient de plus en plus élevée. Le nombre de 5-6 moustiques adopté pour l'exécution de l'épreuve de sensibilité est trop élevé pour avoir une résultat probant et pourtant il y a eu des expériences exécutées même avec 20 moustiques par tube (Wharton, 1955). Nous avons observé qu'en augmentant le nombre de moustiques par tube d'essai les résultats deviennent de plus en plus incertains en ce qui concerne l'action toxique de l'insecticide.

Nos expériences ont montré que toutes les espèces ou races du groupe *maculipennis*, groupées par Buonomini et Mariani (Riv. Malariol., 1953, 32:173) dans le sous-genre *Maculipennia*, en Italie montrent un degré élevé de résistance au D. D. T. En exposant les anophèles au contact soit de solutions de D. D. T. en huile «Risella» soit sur papier filtre pulvérisé avec une solution de D. D. T. en xylole le pourcentage de mortalité est bas, surtout après le contact avec les solutions 2 % en huile «Risella», tandis que sur papier filtre pulvérisé avec solution 2 % de D. D. T. en xylole (correspondante à 2.10 g par mètre carré) la mortalité monte, mais le pourcentage des anophèles tués est en général plutôt bas et ne s'approche jamais au 50 %.

La mortalité moyenne dans les deux types d'expériences de contact a été la suivante pour le groupe *maculipennis*[1]:

A. maculipennis maculipennis: D. D. T. 2 % en huile «Risella»: 2,56 %; D. D. T. 2 % en xylole: 3,7 %.
A. labranchiae: D. D. T. 2 % en huile «Risella»: 5 %; D. D. T. 2 % en xylole: 30,5 %.
A. labranchiae var. *atroparvus*: D. D. T. 2 % en huile «Risella»: 3 %; D. D. T. 2 % en xylole: 22,7 %.
A. sacharovi: D. D. T. 2 % en huile «Risella»: 4,5 %; D. D. T. 2 % en xylole: 23 %.

Les pourcentages de mortalité ont été presque nuls en faisant usage comme solvent du D. D. T. de l'huile «Risella»; ils sont très bas aussi en faisant usage comme solvent du xylole. Cependant la mortalité n'a jamais été élevée, surtout dans les expériences exécutées avec les deux vecteurs *A. labranchiae* et *A. sacharovi*. En augmentant la dose de D. D. T. dans les deux solutions jusqu'à 4 % on obtint des taux de mortalité plus élevés, mais encore bien au dessous du 100 %, car ils s'approchèrent au 50 % seulement dans les expériences faites avec la solution de D. D. T. en xylole, tandis qu'ils se sont seulement accrus légèrement en usant la solution en huile.

Mais comme un des but de ces expériences devrait être celui d'établir quelle est la mortalité des anophèles au contact avec les parois des pièces pulvérisées avec un maximum de 2 g par mètre carré, ce sont les expériences faites avec les solutions 2 % de D. D. T. en xylole qui correspondent mieux à ce qui se passe en pratique. Mais en usant ces dernières la mortalité a été basse et si une heure de contact forcé dans le tube d'essai n'est pas suffisante à tuer les moustiques on se demande qu'arrive-t-il sur les parois pulvérisées où le moustique est libre de s'éloigner aussitôt qu'il ressent les premiers troubles dûs à l'action du toxique? Il est tout à fait probable qu'il s'en éloigne en abbandonant les habitations pulvérisées.

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[1] Pour faciliter l'exposition *A. sacharovi* a été inclus dans le groupe *maculipennis*.

Cependant dans les expériences de contact les anophèles montrent tous les symptomes du poison: paralysie des pattes, agitation et, enfin, ils sont «knock down». Pendant la période d'agitation et de incoordination des mouvements ils viennent en contact avec presque tout leur corps avec le D. D. T. du papier filtre et ils doivent en absorber une quantité bien plus élevée que avec le simple contact des extrémités des pattes, comme il arrive sur les parois pulvérisées.

A différence des espèces du groupe *maculipennis, A. superpictus* s'est montré bien plus sensible au D. D. T. et les taux de mortalité obtenus aux épreuves de contact ont été très élevés; jusqu'à 100 % (en moyenne 92,5 % avec les solutions 2 % en xylole et 51 % avec les solutions 2 % en huile «Risella»).

A. claviger aussi a montré un degré de sensibilité plus élevé des adultes du groupe *maculipennis,* en moyenne 38 %, avec un maximum de 57 % au contact avec la solution 2 % de D. D. T. en xylole.

La souche de *A. stephensi* de notre insectaire a donné des taux de mortalité entre 90 et 97 %.

Les modifications que nous avons apportées à la technique de Busvine et Nash ne réduisent donc pas toujours la mortalité, qui est très haute pour certaines espèces. M. Coluzzi (1958) en Somalie a essayé les mêmes méthodes sur les espèces locales en différentes localitées; pour l'épreuve de contact il a usé seulement les solutions en huile en obténant des maximums de mortalité de 50 % pour *A. gambiae* et de 85 % pour *A. funestus;* il est probable que la mortalité aurait été proche du 100 % au contact avec les solutions 2 % en xylole, comme il est arrivé dans les autres expériences.

La variabilité des taux de mortalité observée dans les différentes expériences a été en rélation à l'âge des moustiques, à la température et à la saison. Nous avons observé (Raffaele et M. Coluzzi, 1957) que les mortalités les plus élevés ont été atteintes en exposant au contact les anophèles capturés au mois de mars, c'est à dire quand la plupart des moustiques sont à la fin de l'hibernation et l'âge les rend plus sensibles au D. D. T. En effet la mortalité a baissé dans les mois où la reproduction des anophèles est très active et il y a beaucoup d'individus jeunes, tandis qu'elle garde à peu près les mêmes valeurs quand la production baisse à cause du tarissement d'une partie des gîtes larvaires et les anophèles qu'on capture sont d'âge différent et les individus jeunes représentent un pourcentage presque constant.

D'après les recherches sur la sensibilité au D. D. T. des différentes espèces d'anophèles en Italie on devrait penser que les espèces plus sensibles devraient disparaître plus facilement, mais en réalité il n'en est rien. Presque partout où il y avait *A. superpictus* on ne le trouve plus, ni dans les maisons ni dans les étables pulvérisées, mais on en trouve toujours en quantité considérable dans les gîtes larvaires. Nous le trouvons dans plusieures localités de 18 sur 38 provinces d'Italie examinées et nous trouvons partout *A. claviger* qui s'est revélé plus sensible au D. D. T. des anophèles du groupe *maculipennis*.

Au contraire les espèces moins sensibles au D. D. T., comme *A. labranchiae* et *A. sacharovi,* ont disparu de plusieures zones jadis très malariques, surtout le long du littoral thyrrénien. Peut être les travaux d'assainissement en ont aidé la disparition. Mais les deux vecteurs persistent en grand nombre dans les provinces de Taranto, Foggia et Matera, où l'on a fait aussi des travaux d'assainissement. *A. labranchiae* persiste nombreux aussi dans les provinces de Cosenza et de Lecce; dans cette dernière représente la seule espèce présente du groupe *maculipennis*.

A. maculipennis maculipennis, très tolérant au D. D. T., on le trouve presque partout, comme *A. claviger,* qui est moins tolérant.

D'après les recherches que nous avons faites la sensibilité d'une espèce à l'insecticide n'est pas une condition qui en assure la réduction ou la disparition. Peut être c'est une erreur de mettre la sensibilité sur le même plan de la mortalité, car en effet toutes les espèces de nos expériences étaient sensibles au D. D. T., car elles ressentaient de son effet toxique; c'était la mortalité qui était variable.

Ce qui est important c'est que les anophèles abbandonnent toute pièce pulvérisée et n'ont que de rares occasions de piquer l'homme, ce qui est suffisant à interrompre la transmission et à éradiquer le paludisme.

A cet égard il n'y a aucune différence entre les régions où les vecteurs persistent et celles où les vecteurs ont disparu et peut être que le danger de la résistance n'est pas aussi grand comme en général on le croit.

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GENERAL DISCUSSION

Dr. L. Bruce-Chwatt (U. K.) — (À propos de MacGregor and Parent) — The speaker emphasized the importance of the work on host-parasite relationship in malaria carried out in the Gambia by Dr. MacGregor's team.

The speaker was most interested in the figures produced by Dr. Parent and inquired whether the changed socio-economic conditions and the use of antimalarial drugs have not played some part in the remarkable decrease of malaria in the area under discussion.

Dr. J. Hamon (France) — Je désire souligner que bien que la région du Sokoto Occidental soit assez proche de celle de Bobo Dioulasso, elle est en fait beaucoup plus comparable à celle de Thiés, au Sénégal, traitée au D. D. T. depuis janvier 1953. Dans cette vaste campagne antipaludique du Sénégal on a enregistré également une quasi interruption de la transmission. Cependant les études récentes du Dr. Escudié ont montré que dans des microclimats favorables, le long de certains marigots permanents bordés de manguiers, où même de palmiers à huile (en pleine zone sahélienne), il se maintien une transmission résiduelle due à *A. funestus*. En saison des pluies ces microclimats favorables permettent pendant quelques mois la réapparition des anophèles dans des zones plus vastes, où *A. funestus* était déjà devenu excessivement rare en 1955.

Dr. Marcel Parent (Congo Belge) — En réponse au Dr. Bruce-Chwatt je signale que le seul changement apporté à la lutte antipaludique en 1948 a été l'introduction de D. D. T.

Nous pouvons donc dire que les améliorations obtenues en 1956 sont dues uniquement à ce D. D. T.

Harry Munro Archibald — At the behest of Dr. L. J. Bruce-Chwatt, I add these few points to those presented in our joint paper.

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The control campaign in Western Sokoto now covers 550,000 inhabitants and an area of about 7,000 sq. miles. As I have returned from there very recently, I can give you up-to-date information of its success.

The infant spleen rate is zero throughout the area of what was the pilot project, and the infant crude parasite rate is zero in the area of that pilot project, except where resistance of *A. gambiae* had become predominant. There the infant parasite rate is 9.5 %. For age groups 1 and 2 years and 3 and 4 years, the parasite rates are now 20 % and 33 % respectively except again in the area where resistance predominated where these rates are 39 % and 69 % respectively.

The average anopheles densities throughout the area of the enlarged campaign are less than 1 female vector per 100 huts.

This represents a very large measure of control but is short of interruption of transmission as is known from the finding of parasites in young children from even the centre of the pilot project whose blood were negative earlier in the year.

This relative success has created an atmosphere in Northern Nigeria favourable to further expansion. Is this justified? In a country of slender resources such as Nigeria, expansion will depend in international assistance and so your opinion is important. Is Africa embraced in the universe which the policy of «eradication» implies as awaiting our action?

SECTION 4

MALARIA ERADICATION

1ST SESSION: *Friday, September 12th — 9:00 to 10:30 a.m. Room D*

The meeting was held under the Chairmanship of Dr. Paul F. Russell and Dr. H. N. Trapido.

The Rapporteur was Dr. Fernando Bustamante and the Secretary was Dr. Manuel T. V. de Meira.

The following papers were presented and discussed:

LE PROBLEME MONDIAL DE L'ERADICATION DU PALUDISME A L'ETAT PRESENT

Dr. E. J. PAMPANA

Directeur de la Division de l'Eradication du Paludisme
Organisation Mondiale de la Santé

Il y a cinq ans, lors des derniers Congrès de Médecine Tropicale et du Paludisme à Istamboul, le terme d'éradication du paludisme n'avait même pas été prononcé. On avait beaucoup discuté de la lutte antipaludique par les insecticides, mais c'est ici à Lisbonne que pour la première fois nous voyons qu'une des sections de ces Congrès est spécialement consacrée à l'éradication. Dès maintenant, on procède à l'éradication, on la prépare ou on l'a pratiquement atteinte dans un total de 76 pays ou territoires comprenant une population globale de 1 156 millions.

S'il peut exister quelque doute sur la signification du terme «éradication», je voudrais préciser qu'une éradication du paludisme ne signifie nullement l'éradication des vecteurs. Il signifie l'élimination totale des parasites du paludisme dans une population donnée. Cette élimination se base sur la notion que dans les infections à *P. falciparum* et à

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 456-463, 1959

P. vivax, même non traitées, il n'est plus possible dans la grande majorité des cas de déceler des parasites dans le sang trois ans après qu'elles ont été contractées. Nous savons certes que, pour rares qu'elles soient, des exceptions peuvent cependant exister. Nous savons également que les infections à *P. malariae* durent beaucoup plus longtemps, peut-être toute la vie, mais il est superflu de rappeler que la diffusion de la quarte est beaucoup plus restreinte que celle des fièvres tierces bénignes ou malignes et que sa transmission est beaucoup plus difficile. On peut donc dire, dans la majorité des cas, que si pendant trois ans, dans une population donnée, aucun nouveau cas d'infection paludéenne ne s'est produit, les anciens sujets infectés pourront être considérés comme guéris du point de vue épidémiologique. Les anophèles ne pourront plus transmettre une infection qu'ils ne peuvent pas contracter. Nous pouvons, vous le savez, accélérer cette évolution, et il est inutile de rappeler que les aspersions des habitations par les insecticides à action rémanente réussissent dans une vaste zone du globe à interrompre le paludisme après une ou deux années. Leur coût peu élevé et la relative facilité de leur application en ont rendu l'emploi presque universel.

L'éradication est un but ambitieux et difficile car il faut l'atteindre dans son entier si l'on veut réussir, alors qu'avec la lutte antipaludique classique toute diminution de la transmission est déjà un succès. On peut se demander pourquoi tant de pays, dont la population s'élève à 1 156 millions, en ont adopté le principe. Si le taux de reproduction du paludisme, d'après Macdonald, est inférieur à 1, l'endémie tend vers la disparition. Par conséquent, si la lutte réussit à ramener le taux à moins de 1, il suffirait de la continuer pendant un certain nombre d'années pour voir le paludisme disparaître. Mais cette lutte telle qu'on la conçoit habituellement ne s'étend jamais à la totalité de la zone impaludée du pays et n'est pas suivie par cette surveillance épidémiologique qui est une phase indispensable de l'éradication. Donc, si l'on vient à interrompre la lutte, les sources d'infection qui subsistent suffisent à ramener rapidement le taux de reproduction à 1 ou au-dessus de 1. On se trouve ainsi devant la nécessité de continuer cette lutte sans arrêt, ce qui se heurte à des difficultés croissantes, car la morbidité ayant été très largement réduite dans le pays, la tentation d'éviter des frais, somme toute élevée, devient de plus en plus forte sous la pression même de l'opinion publique, qui, oublieuse de ce que représentait naguère le paludisme pour l'ensemble de la collectivité, se borne à remarquer que les pulvérisations d'insecticides, si dramatiquement efficaces au début, sont maintenant incapables de détruire les mouches et les punaises! En conclusion, si l'on rejette la politique de l'éradication, on devra suivre celle de la lutte antipaludique, sachant bien qu'il faudra l'arrêter à un moment donné sous l'empire des circonstances et qu'alors l'endémie reprendra et que son retour pourra même se traduire par une épidémie.

Mais nous savons tous que l'argument majeur qui a amené à choisir la politique de l'éradication est le développement de la résistance aux insecticides chez certaines espèces d'anophèles. Cette politique permet d'arrêter la campagne avant que l'insecticide ne soit devenu inefficace. Ce changement de stratégie dans la lutte antipaludique dans le monde fut accepté par la Quatrième Conférence sanitaire panaméricaine à Santiago du Chili en 1954 et l'année suivante par la plus grande instance sanitaire internationale, la Huitième Assemblée Mondiale de la Santé.

Depuis lors, l'UNICEF (Fonds International de Secours à l'Enfance), l'ICA (c'est-à-dire la Division de Santé Publique de l'Administration de Coopération Internationale des Etats-Unis d'Amérique), et la plupart des gouvernements des pays où sévit le paludisme ont adopté l'éradication comme but de leurs efforts. Le Comité d'experts du Paludisme de l'OMS en 1956 donne, dans son Sixième Rapport, un guide pour l'éradication; un grand nombre de réunions de paludologues dans le monde entier ont été consacrées à ce même sujet.

Pour obtenir l'éradication, la méthode est simple: on emploie les insecticides à action rémanente comme pour la lutte antipaludique, mais en traitant toutes les maisons de tout le territoire où la transmission du paludisme a lieu, si faible soit-elle. Après trois ou quatre ans pendant lesquels la transmission a été ainsi interrompue, les pulvérisations insecticides peuvent cesser pourvu qu'on ait déjà mis en oeuvre un système de surveillance convenable, à savoir un dépistage soigné de tous les cas suspects de paludisme comportant un examen de sang, le traitement immédiat des malades et les investigations épidémiologiques nécessaires.

Si l'OMS s'est ralliée à la politique d'éradication du paludisme, que fait-elle pour la réaliser? Elle donne des avis techniques, tant par ses comités d'experts que par ses techniciens, paludologues, entomologistes, agents sanitaires, etc., aux pays qui en ont besoin. Cette année, les spécialistes employés par l'OMS dans le domaine du paludisme dans l'ensemble du monde sont au nombre de 342. Le personnel spécialisé faisant défaut dans beaucoup de pays, l'Organisation a assuré la formation d'une grande partie du personnel international et a naturellement apporté son aide à l'organisation locale de cours destinés au personnel national. Parfois, l'Organisation envoie aussi du matériel — insecticides, véhicules, matériel de laboratoire — si le pays intéressé en a besoin et ne peut l'obtenir par l'intermédiaire de l'UNICEF ou de l'ICA. Enfin, elle s'attache à stimuler et à coordonner les recherches sur des problèmes intéressant de près l'éradication.

Sans considérer les fonds provenants de l'UNICEF, cette année l'Organisation envisage de dépenser pour le paludisme environ six millions et demi de dollars, auxquels il faut ajouter deux autres millions environ, qui seront dépensés par le Bureau Sanitaire Panaméricain, Bureau régional de l'OMS pour l'Amérique. L'an passé, en 1957, le total fut d'un million et un quart et d'environ un million respectivement. Les augmentations de 1958 sont dues aux contributions des gouvernements aux fonds spéciaux pour l'éradication, et particulièrement à celle des Etats-Unis (sept millions de dollars en tout). Sur la base de ces contributions, il a été possible de préparer un plan d'assistance à un programme global d'éradication. Ce plan, commencé en 1958, pourra être mené à bonne fin si ses besoins sont couverts par des contributions supplémentaires au cours des années à venir.

Que l'éradication soit une entreprise très difficile, personne n'en doute: et il n'est pas dans mon intention de vous en décrire les difficultés. Nous avons d'ailleurs vu les raisons qui justifient et rendent même nécessaire que la lutte antipaludique ait pour but l'éradication du paludisme. Cela ne veut pas dire que nous sachions déjà tout ce qu'il faudrait savoir pour établir des techniques scientifiquement démontrées. Il y a de nombreux problèmes dont l'intérêt était peut-être tout à fait secondaire avant que l'on eût pris l'éradication comme objectif, mais qui deviennent maintenant fort importants. Une grande partie ne peuvent être étudiés que sur le terrain et nous ne les mentionnerons pas ici. Par contre, je voudrais définir ici les principaux problèmes à élucider dans les hôpitaux et les laboratoires, dans l'espoir que les chercheurs qui nous écoutent puissent s'y intéresser et les résoudre.

1. La parasitologie même du paludisme présente pour nous des lacunes. Si nous pouvons dire que les infections à *P. falciparum,* à *P. vivax* et à *P. ovale* ont bien peu de chances de persister, du moins

dans le sang circulant, trois ans après leur début, nous aimerions savoir ce qu'il en est des infections à *P. malariae*. Il n'y a pas de doute que ces infections peuvent persister des dizaines d'années, peut-être même toute la vie, et qu'elles peuvent donner des rechutes des dizaines d'années après leur début. Est-ce à dire qu'un sujet infecté par *P. malariae* risque d'infecter les moustiques pendant toute cette période? Nous savons tous comme il est difficile, en laboratoire, d'infecter les anophèles avec ce parasite, de sorte que nous nous rendons compte que des résultats négatifs n'auraient pas beaucoup de valeur. Mais il serait du moins intéressant de faire des observations suivies sur la présence de gamétocytes chez les sujets infectés.

2. D'une façon plus générale, il serait avantageux de suivre également ces cas d'infection à *P. vivax* ou à *P. falciparum* qui ont une durée exceptionnellement longue, et de voir si des gamétocytes sont aussi présents pendant les parasitémies tardives et si les moustiques peuvent s'infecter.

Malheureusement, les possibilités de ces études deviennent sans cesse moins nombreuses, car dès que ces infections à longue durée sont dépistées, on s'efforce généralement, dans les campagnes d'éradication, d'en obtenir la guérison radicale et nous ne voudrions pas suggérer de laisser sans les traiter certains individus qui pourraient autrement continuer à infecter les moustiques.

Ce sont les instituts où l'on fait encore de la malariathérapie qui nous semblent équipés pour de telles recherches, ou encore les instituts qui peuvent disposer de volontaires.

3. Pendant la période de consolidation, quand les opérations de pulvérisation d'insecticides sont terminées et que le service de surveillance épidémiologique représente la seule protection de la population, les sujets susceptibles d'être dangereux et dont il convient d'examiner le sang pour les soumettre éventuellement à un traitement sont ceux qui ont eu récemment de la fièvre.

Nous savons tous qu'il y a beaucoup de porteurs de parasites parfaitement sains et que cela se vérifie dans des zones non seulement à forte hyperendémicité, mais aussi dans un pays aussi hypoendémique que les Pays-Bas. Ces porteurs sains, qui ne peuvent pas être découverts par les opérations de surveillance, passive ou active, peuvent être dépistés par des examens hématologiques de toute la population. C'est là d'ailleurs un test auquel on peut recourir pour vérifier l'efficacité de toute la méthode de dépistage.

Or, il ne faut pas s'arrêter à la constatation qu'un certain nombre de sujets sains, échappant par conséquent à la «surveillance», ont été trouvés porteurs de parasites: il faut évaluer leur danger pour la collectivité et savoir s'ils sont infectieux pour les anophèles.

4. Pour toutes les études que nous venons de proposer, nous nous rendons compte que la simple recherche de gamétocytes peut être insuffisante car nous savons que le moustique est parfois plus habile que le microscopiste à trouver les gamétocytes. Il serait fort utile de trouver une technique qui renverse ce rôle et qui permette de conclure par exemple que la probabilité qu'un sang donné contienne deux gamétocytes dans la quantité correspondante à celle que le vecteur peut sucer est inférieure à 0.01 ou même moindre encore. Quand on l'aura obtenue, l'étude des deux problèmes précédents en serait bien facilitée.

5. Si l'éradication du paludisme dans le monde est appelée à réussir, ce sera non seulement grâce à l'usage des insecticides à action rémanente, qui pourront l'éliminer dans la plus grande partie du monde, mais également grâce à l'usage des médicaments qui pourront nettoyer certaines «poches» où les insecticides seuls seraient insuffisants et rendre non infectieux les cas résiduels. Aujourd'hui, la difficulté principale dans le domaine des médicaments est celle de leur application. Elle serait beaucoup facilitée si les antipaludiques nécessaires pouvaient être distribués dans le sel, ainsi que Pinotti le proposa aux Congrès d'Istamboul. Coatney a confirmé les résultats de Pinotti, en les étendant au sel pyriméthaminisé: mais cette méthode exige que la population à laquelle elle est destinée n'ait pas la possibilité de s'approvisionner d'un autre sel que celui additionné d'antipaludiques. L'administration des médicaments serait aussi facilitée si on pouvait les utiliser comme on se sert de la pénicilline dans les campagnes contre le pian. Si l'on pouvait trouver une préparation qui reste active pendant quelques mois, soit par voie orale, soit par voie parentérale (ce qui pourrait être un avantage chez certaines populations), nous aurions là un autre moyen puissant pour obtenir l'éradication. On suppose que l'action sporontocide de la pyriméthamine persiste pendant plusieurs semaines après son administration, mais il existe très peu de publications sur ce sujet et il faut souhaiter que cette action sporontocide de la pyriméthamine ainsi que celle de la primaquine puisse être étudiée sur un grande nombre

de sujets et de souches de parasites. Si chaque sujet soupçonné d'être porteur de parasites pouvait recevoir un médicament le rendant non infectieux pour les anophèles pour quelques semaines, les services d'éradication du paludisme verraient leur tâche bien simplifiée. Dans plusieurs campagnes d'éradication, les cas suspects reçoivent immédiatement une dose unique de chloroquine et de pyrimétamine et nous croyons que cette prescription est la meilleure que l'on puisse choisir aujourd'hui. Mais nous aimerions avoir des données pouvant mieux la justifier.

6. Dans le domaine de l'entomologie, il y a encore une foule de problèmes qui sont pour la plupart inhérents à une espèce donnée ou à une région donnée. D'ordre général sont par contre ceux qui se réfèrent au problème de la résistance, de son mécanisme, de la génétique et sur lesquels ces Congrès entendront sans doute des orateurs fort compétents.

7. Mais le chimiste pourrait apporter une contribution de grande valeur aux campagnes d'éradication en étudiant certains problèmes qui, jusqu'à maintenant, n'ont reçu que peu d'intérêt. Le phénomène de la «sorption» constaté sur certains murs de terre et par lequel les insecticides disparaissent des surfaces traitées après quelques jours seulement ne saurait être tenu pour négligeable en ce qui concerne l'efficacité des pulvérisations. C'est au chimiste d'étudier les moyens d'y remédier, soit par un traitement préalable des surfaces, soit par la mise au point de préparations insecticides moins «sorbables».

8. La collaboration des chimistes nous serait aussi fort précieuse pour la mise au point de méthodes permettant d'attaquer les anophèles devenus résistants à un insecticide donné. Il conviendrait de trouver soit des substances qui, ajoutées à l'insecticide, le rendent à nouveau léthal pour l'insecte, soit d'autres produits insecticides, par exemple de la série du phosphore organique, doués d'un pouvoir rémanent et d'une toxicité comparable à celle du D. D. T.

Les quelques problèmes que je viens d'indiquer vous montreront qu'il y a encore du travail de recherche à faire dans les instituts et les laboratoires dans le domaine du paludisme. Malheureusement, peu d'instituts s'y intéressent. L'Organisation s'efforce d'obtenir la collaboration des chercheurs dans le monde entier et, dans les projets qu'elle assiste, surtout en Afrique, de leur imprimer un caractère expérimental. Si l'on fait le total des sommes que l'Organisation, en 1958, dépense pour la recherche dans le domaine du paludisme, dans les laboratoires ou sur le terrain, comme dans les projets auxquels je viens de faire allusion, on arrive à la somme de $ 834 588. Mais cela n'est pas suffisant. Si j'ai abusé de votre temps pour vous présenter une communication à caractère peu scientifique, c'est pour vous mettre au courant des efforts que l'O. M. S. fait dans le domaine du paludisme et, d'autre part, pour exprimer l'espoir que ceux de vous qui en ont la possibilité veuillent bien mettre à l'étude certains des problèmes que je viens de décrire.

ERADICATION OF MALARIA IN THE AMERICAS STRATEGY AND ORGANIZATION

Carlos A. Alvarado, Patrick N. Owens
and Tito Lopes da Silva[1]

The concept of eradication of malaria was born with Ross, who worked on the mathematics of malaria eradication without mosquito eradication. But, in general, rural malaria defied attempts at reasonably economic control, and, only two decades ago, Boyd, in his Presidential Address to the American Society of Tropical Medicine, was willing to settle for «building out» malaria from year to year, through long term local programs.

Health workers in other fields had spoken boldly of eradication, but the concept itself was abandoned by an entire generation of health workers in the face of continued failure and frustation.

Hopes for eradication of species, either disease-bearing organisms, or causative agents themselves, began to revive in the Americas following the successfull eradication of *Aedes aegypti* from Brazilian cities, and the eradication of *Anopheles gambiae* from Brazil and Egypt.

The introduction of D. D. T., which made the human dwelling the determining parameter for calculating unit costs, rather than the surfaces of anopheline breeding places, made the antimalaria compaigns technically and economically feasible. All control programs began to be expanded, thus lowering mortality, morbidity, and all malarial indices, but demonstrating at the same time that.

Eradication is not a simple extension of control unless control is of an unusually high order of efficiency and perfection; must include, initially, fairly large areas; and expand at the periphery without regard to international boundaries.

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[1] From the malaria eradication unit, Pan American Sanitary Organization, Washington 6, D. C.

The initial euphoria, and the amount of annual malaria budgets, began to decline at approximately the same time that anopheline resistance began to appear. Although some of the countries with leading places in the eradication movement had demonstrated the practicability of malaria eradication, it was not until the Pan American Sanitary Organization and the World Health Organization had developed into organizations with the confidence of the national health authorities and with the ability to coordinate work in all countries of a geographical region, that a hemispheric, and later, a world movement toward eradication became apparent and consistent.

A short historical summary will show the succession of events in malaria eradication, as they occurred in the Americas:

1 — In 1947, the Congress of the United States voted funds for «The National Malaria Eradication Program».

2 — In 1948, British Guiana reported the eradication of the vector of malaria, *A. darlingi*, from the coastal zones.

3 — A reconnaissance of the malaria control programs in the Americas was made in 1950 for the XIII Pan American Sanitary Conference, with recommendations for eradication programs to be begun immediately. The Conference, meeting in October of the same year, supported the eradication concept, but the countries were neiter psychologically ready, nor was the P. A. S. B. economically able to implement the resolutions of the Conference.

4 — In November of the same year, a symposium on malaria eradication was held in Savannah, Georgia, U. S. A., sponsored by the National Malaria Society. At the same meeting, the N. M. S. established the criteria for malaria eradication and voted to disband itself.

5 — In 1954, Venezuela reported the first large area of malaria eradication within the tropical regions.

6 — A new reconnaissance of the status of the malaria programs in the Americas was made in 1954 again under the auspices of the Pan American Sanitary Bureau. It showed both a lack of consolidation and progress, and a frank deterioration of the National Malaria Services over the situation obtaining in 1950; and that in the face of the possibilities of resistance in vector species. This picture was presented to the XIV Pan American Sanitary Conference at Santiago, Chile, in October, 1954, and a strong resolution was passed declaring that it was of the

utmost urgency to carry out the terms of the previous resolution of the XIII Conference, recommended to member governments the conversion of control programs into eradication campaigns and instructed the P. A. S. B. to implement the aforesaid resolution, to establish an emergency fund for administrative purposes, and authorized the creation of a special voluntary eradication fund.

7 — In January, 1955, the Presidente of Mexico, a country considered at that time as one of the principal reservoirs of malaria transmisssion in the Americas, authorized the preparation of a nation-wide malaria eradication plan, to be supported with extra-budgetary funds and long-term financing, but later supported with regular budgetary funds.

8 — In March, 1955, the Executive Board of the International Childrens' Fund (U. N. I. C. E. F.), subject to the technical recommendations of the U. N. I. C. E. F.-W. H. O. Joint Committee on Health Policy, decided to endorse the general proposition that U. N. I. C. E. F. provide increased aid to enable governments to intensify their control programs in order to achieve malaria eradication.

9 — Early in May, 1955, the Joint Committee on Health Policy recommended that U. N. I. C. E. F., in giving aid to new antimalaria projects, should give first priority to eradication programs, and established the basic conditions under which such aid might be obtained.

10 — A few days later, the VIII World Health Assembly, meeting in Mexico City, approved a resolution for the development of a coordinated program for the eradication of malaria throughout the World, and authorized the creation of a malaria eradication special account.

11 — In September of 1956, the Government of the U. S. A., having become more and more interested in malaria eradication, announced a contribution of $ 1,500,000 for the Special Malaria Fund of the PASB. Early in 1957, the Dominican Republic contributed $ 100,000 as the first payment on a pledge of $ 500,000 to the Special Malaria Fund, and Venezuela gave a contribution of $ 300,000.

12 — In mid-1957, the Congress of the U. S. A. made a specific appropriation for World-wide malaria eradication, through the International Cooperation Administration of that Government. A significant part of this appropriation was channelled through the international agencies and the balance through separate bilateral agreement with the governments concerned.

With the first administrative fund ($ 100,000) authorized by the XIV Pan American Sanitary Conference, the Bureau organized and established a special coordinating office for the malaria eradication programs, located, initially, in Mexico City, and gave to it the responsability of preparing operating standards and developing the strategy for the continental plan.

These operating standards were given in a series of documents known by the title of «PASB/COMEP Documents», which, reviewed and approved by the PASB Advisory Committee on Malaria Eradication, constituted the framework for technical program planning. This planning, as developed in the Americas, consisted of the following points:

1) Preparation of an initial plan of operations as detailed and perfect as possible.

2) Creation in each country of a «National Malaria Eradication Service» at a high level within the governmental structure; and provision of full administrative authority and an adequate and well trained staff;

3) Enactment of appropriate legislation for the program;

4) Adequate financing for the entire period of the program;

5) Development of the plan of operations in three phases:

preparatory (or conversion from control), 1 year;
full attack, 4 years; and
consolidation, 3 years;

6) Execution of all operations, from the very beginning, throughout the entire endemic malarious area;

7) Production of a great impact on the general public psychology through an intensive campaign of health education and information; which both awakens interest and obtains public support;

8) Promotion of collaboration of all governmental agencies (public health services, schools, armed forces, etc., etc.) as well as ecclesiastical and private organizations, and the general public;

9) Rigourous supervision of all operations, judging them not so much by what has been done, as by what still needs be done;

10) Epidemiological evaluation of results, related to ZERO, from the moment of beginning total coverage with insecticides. For this evaluation, the creation of a department of epidemiology is a *sine qua non*; and the department must be provided with the necessary material,

transportation and personnel for carrying out its function, which, in the main, will consists of the systematic search for malaria cases, through a network of community collaborators and by house-to-house visits.

This operational methodology, as just described, has not been followed in all of its implications in all the malaria services of the Americas; however, in each governmental unit efforts have been made, and are continuing, to adjust the national programs into the general lines as listed above.

The integration of the hemisphere-wide plan also to the object of strategic planning, above all with relation to activities by the international agencies involved. This plan included, among other items, the following:

1. Organization of a large scale training effort in all activities related to malaria eradication, and at all levels of the services. The existing facilities, offered for many years by the Government of Venezuela at Maracay, were utilized to the fullest, but the pressure of the training requirements was so great that additional centers have been established in Mexico City, Kingston (Jamaica) and São Paulo (Brazil).
2. Maximum utilization or any program which offered possibilities for demonstration of techniques, and awarding of travel grants to key personnel of all services so that maximum advantage of these facilities might be taken.
3. Reinforcement of the technical advisory services by the international agencies, assigning to each eradication program a medical officer and an engineer, both trained in malaria eradication techniques, as well as a variable number of specialized sanitary inspectors. In addition, supervisory personnel of the international agencies were increased.
4. Other specialized advisory personnel have been appointed, under zonal or regional basis specifically, in the fields of entomology, parasitology, statistic, health education, administrative methods, and vehicle management.
5. Organization of a special unit called the «Evaluation Team», to certify the eradication of malaria at the countries request and to evaluate the efficiency of the epidemiological operations.
6. Organization of seminars, workshops, and meeting of several kinds, of which particular mention should be made of the meeting of Directors of Malaria Eradication Services of neighbouring countries. These

meeting have unified the technical approach, and the frank and free review of progress and difficulties; the development of methods and procedures which result from these meeting, and which spring spontaneously from the services themselves are among the most stimulating examples of the desire of the countries for a dynamic and productive approach to the perfection required by eradication programs.

7. The stimulation and maintenance of a spirit of singleness of purpose in the continental plan for eradication, in which the plan in each country is considered by that country as part of a hemisphere-wide effort. This spirit of corps is being achieved in great part, through the regional meeting of directors and their chief advisers and executive officers, in which meeting as already mentioned, there exists a singular atmosphere of give-and-take during the discussions, and a fruitful comradeship in attacking common problems.

The fact that eradication programs began almost simultaneously in several countries, and that the PASB received significant contributions to its Special Malaria Fund, have modified both the amount and the character of its antimalaria work. From what initially was a purely technical advisory capacity for the planning of programs, the Bureau has been obliged to grapple with problems of organization, of administrative implications in all phases of the programs, of training on a large scale, both of national and international personnel, of the provision of essential supplies and materials, and, at times, of direct financial assistence to certain countries. The multiplicity of problems obliged the director to transfer the malaria unit from Mexico City to the regional headquarters in Washington.

Before passing to a consideration of the progress and actual status of the programs in the Americas, it might be well to state that although difficulties have arisen at several stages in a number of the countries, these are being overcome as rapidly as possible. It may be interesting for reprentatives of other regions of the world to learn that one of the consistent errors in planning malaria eradication programs in the Americas has been the underestimation of the magnitude of the problem in terms of the population at risk. Ordinarily this estimation is made on the basis of census data, projected for the years following. But it would seem that previous malaria control, in many countries, had been so successful that population growth in previously malarious areas has exceeded the demographers' expectations. Such data have often been determined only after the operations of geographical reconnaissance.

The important thing to record for this group today is that as these errors and difficulties become apparent, they are attacked and corrected by the countries and the internationel agencies, so that their effects are minimized or nullified.

Another difficulty already presenting itself is that of anopheline resistance. During the investigation of several persistent foci of transmission in El Salvador three months ago, the entomologists Duret and Heredia found a high level of physiological resistance by *A. albimanus* to Dieldrin, and a moderate level of resistance to D. D. T.

The present status of the eradication program of the Americas may be appreciated from a consideration of the tables which we will show which have been taken from the VI Report on the malaria situation, prepared for the XV Pan-American Sanitary Conference, to be held in San Juan, Puerto Rico, within the month.

Table no. 1 shows the countries or political units in which malaria is either unknown historically, or from which it has disappeared without specific eradication measures.

TABLE 1 — *Countries and other political units in which malaria is not known to have occurred or has disappeared without specific eradication measures*

Country or other political unit	Area in km²	Estimated population as of 1 July 1957
Total	*10 187 740*	*19 877 000*
Canada	9 974 375	16 589 000
Uruguay	186 926	2 690 000
Antigua	442	55 000
Bahamas	11 396	120 000
Bermuda	53	42 000
Falkland Islands	11 961	2 000
Montserrat	83	17 000
Netherland Antilles	961	190 000
St. Kitts-Nevis-Anguilla	396	55 000
St. Pierre and Miquelon	240	5 000
St. Vincent	389	80 000
Virgin Islands (Br.)	174	8 000
Virgin Islands (U. S. A.)	344	24 000

Table no. 2 shows countries and other political units from which malaria has been eradicated. It will be seen that the larges portions of the population of 45 014 000 living in areas from which malaria has been eradicated, corresponds to that in the U. S. A. and Puerto Rico.

TABLE 2 — *Countries and other political units where malaria has been eradicated*

Country or other political unit	Area in km²	Population	Original malarious areas	
			Area in km²	Population
Total	*10 098 948*	*179 993 000*	*2 322 691*	*45 014 000*
Chile	741 767	6 681 000	55 287	112 000
U. S. A.	9 346 751	170 547 000	2 257 809	42 366 000
Barbados	431	230 000	430	228 000
Martinique	1 102	255 000	300	45 000
Puerto Rico	8 897	2 280 000	8 865	2 263 000

Table no. 3 is a combination of table 3 and 4 of the mimiographic paper and expresses the present situation with respect to the other countries and territories. It may be seen that Venezuela contains the largest area from which malaria has been eradicated in these countries, and the largest population freed from the disease.

Table no. 4 is a resumé of the situation presented in map form in the paper. It may be seen that four countries were in the preparation phase as of July 31/58: Brazil, Colombia, Haiti and Nicaragua, and that one country is still without a plan as of that date. However, Haiti began the phase of total coverage with insecticides on September 1, and Colombia is ready to begin on September 8. Brazil plans to begin in January, 1959, with a program of total coverage in three stages, during three successive years; while Nicaragua had begun its program but was forced to suspend operations for administrative reasons, will begin again before December 31.

Only one country, Cuba, has not yet been incorporated into the hemisphere-wide plan, but it is expected to do so as soon as local difficulties can be overcome.

Figure no. 1-*a* shows several of the plans of operations, prepared by the countries, for malaria eradication in the Americas.

Table no. 5 shows the position of the National Malaria Eradication Services within the health structures of the countries. It will be seen

TABLE 3 — *Extent of malarial problem by areas in the Americas, 1958*

Country or other political unit	Total area in km²	Original malarious area in km²	Area with malaria eradicated		Area under surveillance		Area with malaria not yet eradicated	
			Three or more years without indigenous case		Less than three years without indigenous case		Regularly sprayed	Not regularly sprayed (*a*)
			Area in km²	Spraying continued	Area in km²	Spraying continued	Area in km²	Area in km²
Total	*19 539 572*	*12 235 392*	*407 744*		*140 242*		*8 877 996*	*2 809 410*
Argentina	2 778 412	120 000	26 200	No	23 000	No	70 800	—
Bolivia	1 098 581	842 018	—	—	—	—	842 018	—
Brazil (*b*)	8 268 814	7 299 969	611	Yes	—	—	5 958 814	1 340 544
São Paulo	247 223	110 318	—	—	—	—	—	110 318
Colombia	1 138 355	1 026 433	—	—	—	—	—	1 026 433
Costa Rica	50 900	31 526	—	—	—	—	31 526	—
Cuba	114 524	**	**	**	**	**	**	**
Dominican Republic	48 734	41 010	—	—	—	—	41 010	—
Ecuador	270 670	153 498	—	—	—	—	53 098	—
El Salvador	20 000	19 310	—	—	—	—	19 310	—
Guatemala	108 889	80 380	—	—	—	—	80 380	—
Haiti	27 750	21 300	—	—	—	—	—	21 300
Honduras	112 088	87 383	—	—	—	—	87 383	—
Mexico	1 969 269	928 749	—	—	—	—	928 749	—
Nicaragua	148 000	127 199	—	—	—	—	8 126	119 073
Panama	74 470	68 499	—	—	—	—	68 499	—
Paraguay	406 752	42 286	—	—	—	—	42 286	—
Peru	1 249 049	154 191	—	—	—	—	154 191	—
Venezuela	912 050	600 000	372 604	Yes	36 464	Yes	190 932	—
Other political units								
British Guiana	215 800	215 800	4 940	No	—	—	19 760	191 100
British Honduras	22 965	22 965	—	—	—	—	22 965	—
Dominica	789	642	—	—	—	—	—	642
French Guiana	91 000	80 000	—	—	80 000	Yes	—	—
Grenada	344	160	—	—	—	—	160	—
Guadeloupe	1 780	1 136	69	...	752	Yes	315	—
Jamaica	12 188	10 050	—	—	—	—	10 050	—
Panama Canal Zone	1 432	1 438	—	—	—	—	1 438	—
St. Lucia	616	524	—	—	—	—	524	—
Surinam	143 000	143 470	3 320	No	—	—	140 150	—
Trinidad and Tobago	5 128	5 138	—	—	26	No	5 112	—

(*a*) Includes areas not sprayed under a plan of total coverage.
(*b*) Not including the State of São Paulo.
— Nil.
** Report not received.

Country or other political unit	Total population estimate 1957	Population of the original malarious area	Area with malaria eradicated		Area under surveillance		Area with malaria not yet eradicated	
			Three or more years without indigenous case		Less than three years without indigenous case		Regularly sprayed	Not regularly sprayed (*a*)
			Population	Spraying continued	Population	Spraying continued	Population	Population
Total	*177 795 000*	*86 416 000*	*4 531 000*		*1 493 000*		*53 865 000*	*26 527 000*
Argentina	19 858 000	1 473 000	247 000	No	711 000	No	515 000	—
Bolivia	3 273 000	1 102 000	—	—	—	—	1 102 000	—
Brazil (*b*)	58 538 000	29 495 000	638 000	Yes	—	—	19 921 000	8 936 000
São Paulo	2 730 000	2 678 000	—	—	—	—	—	2 678 000
Colombia	13 227 000	9 787 000	—	—	—	—	—	9 787 000
Costa Rica	1 035 000	451 000	—	—	—	—	451 000	—
Cuba	6 410 000	**	**	**	**	**	**	**
Dominican Republic	2 698 000	2 417 000	—	—	—	—	2 417 000	—
Ecuador	3 890 000	1 955 000	—	—	—	—	1 955 000	—
El Salvador	2 350 000	1 385 000	—	—	—	—	1 385 000	—
Guatemala	3 430 000	1 448 000	—	—	—	—	1 448 000	—
Haiti	3 384 000	4 096 000	—	—	—	—	—	4 096 000
Honduras	1 770 000	1 282 000	—	—	—	—	1 282 000	—
Mexico	31 426 000	15 588 000	—	—	—	—	15 588 000	—
Nicaragua	1 331 000	1 071 000	—	—	—	—	95 000	976 000
Panama	960 000	910 000	—	—	—	—	910 000	—
Paraguay	1 638 000	700 000	—	—	—	—	700 000	—
Peru	9 923 000	2 878 000	—	—	—	—	2 878 000	—
Venezuela	6 134 000	4 479 000	3 065 000	Yes	469 000	Yes	945 000	—
Other political units								
British Guiana	515 000	460 000	423 000	No	—	—	34 000	3 000
British Honduras	84 000	82 000	—	—	—	—	82 000	—
Dominica	62 000	51 000	—	—	—	—	—	51 000
French Guiana	29 000	25 000	—	—	25 000	Yes	—	—
Grenada	94 000	26 000	—	—	—	—	26 000	—
Guadeloupe	250 000	210 000	34 000	...	127 000	Yes	49 000	—
Jamaica	1 594 000	1 296 000	—	—	—	—	1 296 000	—
Panama Canal Zone	55 000	40 000	—	—	—	—	40 000	—
St. Lucia	91 000	68 000	—	—	—	—	68 000	—
Surinam	251 000	250 000	124 000	No	—	—	126 000	—
Trinidad and Tobago	765 000	713 000	—	—	161 000	No	552 000	—

(*a*) Includes areas not sprayed under a plan of total coverage.
(*b*) Not including the State of São Paulo.
— Nil.
** Report not received.
... Data not available.

TABLE 5 — *The organization of national malaria services in the Americas, 1957*

Country or other political unit	Official names of service	Position of service	Activities other than malaria eradication
Argentina	Dirección de Paludismo y Fiebre Amarilla	Primary	Campaign for the eradication of *Aëdes aegypti*
Bolivia	Servicio Nacional de Erradicación de la Malaria	Primary	None
Brazil (*a*)			
São Paulo	Campanha de Erradicação da Malária	Primary	None
	Serviço de Profilaxia da Malária (*b*)	Secondary	Prevention of Chagas' disease and schistosomiasis
Colombia	Servicio Nacional de Erradicación de la Malaria	Autonomous	None
Costa Rica	Departamento de Lucha Contra Insectos Transmisores	Primary	None
Cuba	**	**	**
Dominican Republic	División de Malariologia	Primary	Campaign for the eradication of *Aëdes aegypti*; and insect control
Ecuador	Servicio Nacional de Erradicación de la Malaria	Primary	None
El Salvador	División de Lucha Anti-Palúdica	Primary	Anti-*Aëdes aegypti* campaign
Guatemala	Servicio Nacional de Erradicación de la Malaria	Primary	Eradication of *Aëdes aegypti* and vaccination against yellow fever
Haiti	Service National d'Eradicación de la Malaria	Primary	None
Honduras	Servicio Nacional de Erradicación de la Malaria	Primary	Anti-*Aëdes aegypti* campaign
Mexico	Comisión Nacional para la Erradicación del Paludismo	Autonomous	None
Nicaragua	Servicio Nacional de Erradicación de la Malaria	Primary	Anti-*Aëdes aegypti* campaign

(*a*) Not including the State of São Paulo.
(*b*) Soon to be change to «Serviço Especial de Erradicação de Malária».
** Report not received.

TABLE 5 — (Continuação)

Country or other political unit	Official names of service	Position of service	Activities other than malaria eradication
Panama	Servicio Nacional de Erradicación de la Malaria	Primary	Control of yellow fever (vaccination and *Aëdes aegypti* eradication)
Paraguay	Servicio Nacional de Erradicación del Paludismo	Primary	None
Peru	Servicio Nacional de Erradicación de la Malaria	Primary	None
Venezuela	División de Malariologia	Primary	*Aëdes aegypti* eradication, control of Triatomidae, flies, rodents, etc.
Other political units			
British Guiana	Mosquito Control Service	Secondary	*Aëdes aegypti* and bancroftial filariasis control
British Honduras	Health Department	Primary	Yellow fever and other public health activities
Dominica	Anti-Malaria Activities under Sanitary Department	Primary	Insect control in general
French Guiana	Service de la Lutte Antipaludique et Antiamarile	Secondary	Yellow fever campaign and destruction of other anthropods of Public Health import
Grenada	Medical Department	Primary	Other public health activities
Guadeloupe	Service Départemental de Désinsectisation	Secondary	Disinfection and disinsecting in general
Jamaica	Malaria Eradication Programme	Primary	None
Panama Canal Zone	Health Bureau, Canal Zone Government	Secondary	Pest mosquito and culicoides control, all phases of environmental sanitation, and sanitary engineering and entomological support for maritime quarantine
St. Lucia	Malaria Eradication Program	Primary	Anti-*Aëdes aegypti* campaign
Surinam	Malariabestrijdingsdienst	Primary	None
Trinidad and Tobago	Malaria Division	Primary	*Aëdes aegypti* eradication, general insect control and quarantine activities

clearly that the services now enjoy a high stature within the national public health structure. Two countries, Mexico and Colombia, have «autonomous» organizations reporting directly to the Minister of Health, and all others have the N. M. E. in primary position, reporting to the director of Health or his equivalent. This is indeed a great advance over the year 1954 in which 12 countries had their malaria services in secondary rank.

The next table is not possible to project due to its size. It contains a comparative study on malaria legislation. It shows that most of the countries and territories possess special legislation, some with advanced features, such as the compulsory notification of cases within 24 hours with corresponding blood samples; the obligation of patients to submit to treatment and permit blood extraction; reporting of migratory movements of the population; and, in one case, with the prohibition of occupancy of unsprayed premises.

The panorama presented represents a most promising situation. The beginning of the effort may be considered as entirely satisfactory; but it is recognized that only the initial battles in the war have been won: preparation of correct plans; training of personnel; supporting legislation; adequate financing; high position of the services; the beginning of the direct attack; and integration of the hemisphere plan with adequate international advice and assistance. Other battles are being fought: the system of epidemiological evaluation and reporting of cases are being perfected, and the administrative machinery is being modified as required. For the future, there is the test of time itself. First, the completion of the four years of total coverage, without a diminution in the intensity, regularity, and perfection of the operations, which requires protection of the programs against political and administrative contingencies. Secondly, an alertness is required at all levels for the early detection and resolution of the technical problems which will arise with the passage of time. Thirdly, it will be necessary to maintain and intensify the concept of the universality of eradication, the foundation stone for its lasting effects once achieved.

We have chronicled the sequence of events as they have occurred in the Americas, and have sketched some of the fundamentals of strategy and organization as these have developed. There is a further characteristic of the programs in the Americas which we should mention at this time, and it is simply that apart from the scientific facts, the technical

TABLE 6 — *Comparative antimalaria*

Subject	Argentina	Bolivia	Brazil (*a*)	São Paulo	Colombia	Costa Rica	Cuba	Dominican Republic	Ecuador	El Salvador
Has special legislation	x	x	x	x	x	x	**	x	x	x
Obligation to combat malaria	x	x	x	x	x	x	**	x	x	x
Declaration of malarious zones	x	x	—	x	x	x	**	—	—	—
Declaration of the problem as being of national interest	x	x	—	—	x	x	**	x	—	x
Application of the concept of eradication	—	x	x	—	x	x	**	x	x	x
Obligation to apply imagocides	x	x	—	—	—	x	**	x	—	x
Obligation to permit access to houses	x	x	—	x	—	x	**	x	x	x
Obligation to give drugs	x	x	x	x	—	x	**	—	x	—
Control of distribution and dispensing of drugs	x	—	—	x	—	x	**	—	—	x
Obligation to report the construction or renovation of dwellings	x	—	x	—	—	—	**	—	—	—
Compulsory case reporting	x	x	x	x	x	x	**	x	x	x
Time limit (No. of days)	1	1	—	(*c*)	—	1	**	1	(*c*)	1
With blood sample	x	—	—	—	—	x	**	x	—	—
Obligation of patient to take treatment	—	x	—	—	—	x	**	x	x	—
Obligation of patient to permit blood extraction	x	—	—	—	—	x	**	x	—	—
Sanctions	x	x	x	x	—	x	**	x	x	x
Obligation of authorities, firms, and individuals to cooperate	x	x	—	x	x	x	**	x	x	x
Exemption from customs duties	—	x	—	—	x	x	**	—	x	x
Obligation to spray aircraft and ships	—	—	x	x	—	—	**	—	—	—
Postal franking privileges	—	—	—	—	—	x	**	—	—	—
Obligation to report on painting or washing of sprayed premises	—	—	—	—	—	x	**	—	—	—
Reporting on migratory movements	x	x	x	—		x	**	x	—	—
Prohibition against occupancy of unsprayed premises	—	—	—	—	—	x	**	—	—	—
Obligation to carry out environmental sanitation activities	x	x	x	x	x	x	**	x	x	x

(*a*) Not including the State of São Paulo.
(*b*) Information taken from V Report.
(*c*) Immediate reporting but without set time limit.
× Yes.
— Nil.
** Report not received.
... Data not available.

legislation in the Americas, 1958

Guatemala	Haiti	Honduras	Mexico	Nicaragua	Panama	Paraguay	Peru	Venezuela (*b*)	British Guiana (*b*)	British Honduras	Dominica	French Guiana	Grenade	Guadeloupe	Jamaica	Panama Canal Zone	St. Lucia	Surinam	Trinidad and Tobago
x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	...	x	...	x
x	x	x	x	x	x	x	x	x	x	x	—	x	x	—	—	...	x	...	x
—	—	—	—	—	—	—	x	x	—	—	x	—	—	—	—	...	—	...	x
x	x	x	x	x	x	—	x	—	—	—	—	—	—	—	—	...	—	...	—
x	x	x	x	x	x	x	x	—	—	—	—	—	—	—	—	...	—	...	—
x	—	x	—	x	x	—	x	—	x	—	—	x	x	—	—	...	x	...	—
x	—	x	—	—	x	x	x	—	x	x	—	x	x	x	x	...	x	...	—
x	x	x	—	x	—	x	x	x	—	—	—	—	—	—	—	...	x	...	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	...	—	...	—
x	x	—	—	—	x	x	—	—	—	—	—	—	—	—	—	...	—	...	—
x	x	x	x	x	x	x	x	x	x	x	x	—	—	—	x	...	x	...	—
1	1	1	1	1	1	1	7	7	(*c*)	7	30	—	—	—	(*c*)	...	7	...	—
x	x	x	—	x	x	x	—	—	x	—	—	—	—	—	—	...	—	...	—
x	—	x	—	x	x	x	—	x	—	x	—	—	—	—	—	...	—	...	—
—	x	x	—	x	x	—	—	x	—	x	—	—	—	—	x	...	—	...	—
x	x	x	—	x	x	x	—	x	x	x	x	x	x	—	—	...	x	...	x
x	x	x	—	x	x	x	x	—	—	—	—	—	—	—	—	...	—	...	—
—	—	—	x	—	—	—	—	x	—	—	—	—	—	—	—	...	—	...	—
—	—	—	—	—	x	—	—	—	—	—	—	—	—	—	—	...	—	...	—
x	—	x	—	x	x	x	—	—	—	—	—	—	—	—	—	...	—	...	—
—	—	—	—	—	—	x	—	—	—	—	—	—	—	—	—	...	—	...	—
x	—	x	—	x	—	x	—	—	—	—	—	—	—	—	—	...	—	...	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	...	—	...	—
x	—	—	x	—	x	—	x	x	x	x	x	x	x	x	—	...	x	...	x

details, and the strategy, eradication of malaria is being carried out by an extraordinary number of devoted people. For Ministers of Health and microscopists, for spraymen and schoolteachers, for director of services and drivers of vehicles, wiping out malaria once and for all is what they wish to do more than any other thing, and this is the reason for the advanced status of the effort. More and more, in the Americas, the initials D. D. T. stand for Dedication to the concept of eradication; Discipline in the attack, and Tenacity of purpose.

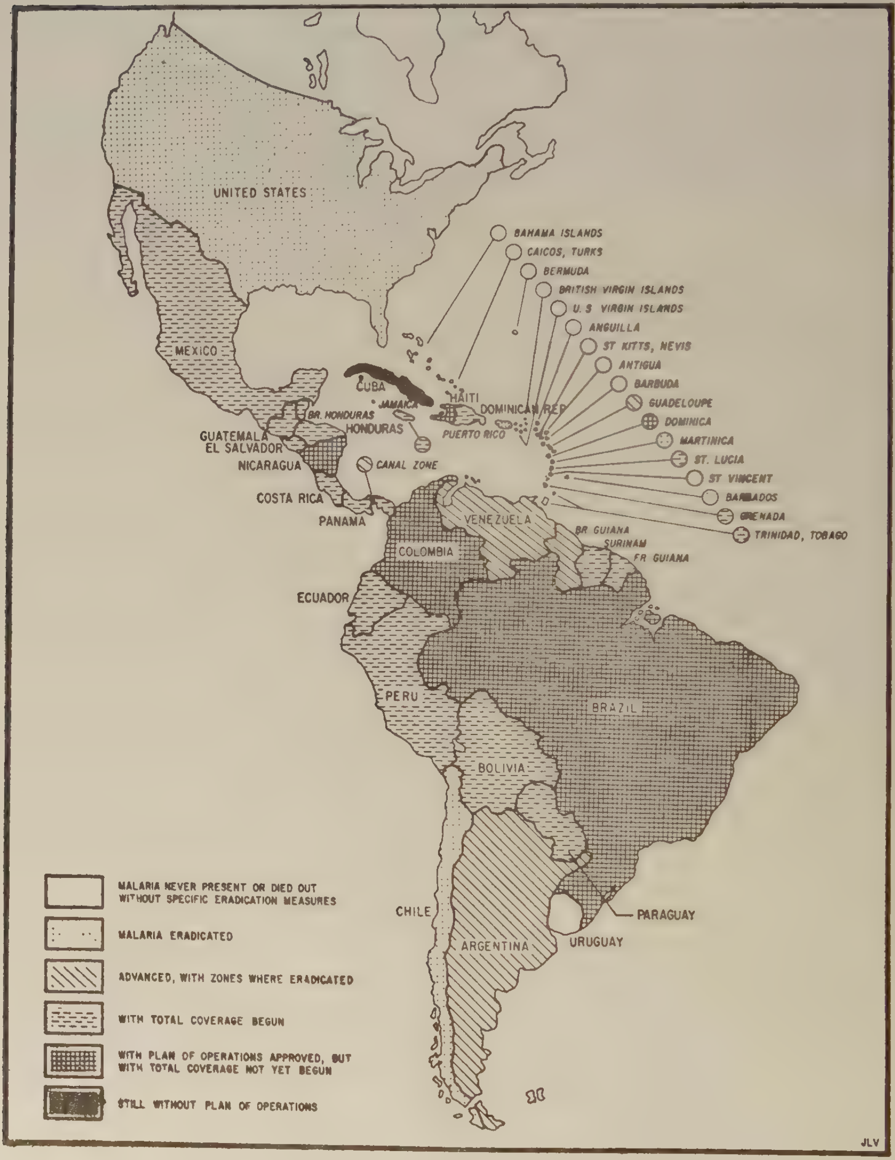

UNITED STATES
MEXICO
CUBA
JAMAICA
HAITI
DOMINICAN REP
PUERTO RICO
BR. HONDURAS
HONDURAS
GUATEMALA
EL SALVADOR
NICARAGUA
COSTA RICA
PANAMA
CANAL ZONE
BAHAMA ISLANDS
CAICOS, TURKS
BERMUDA
BRITISH VIRGIN ISLANDS
U. S VIRGIN ISLANDS
ANGUILLA
ST KITTS, NEVIS
ANTIGUA
BARBUDA
GUADELOUPE
DOMINICA
MARTINICA
ST. LUCIA
ST VINCENT
BARBADOS
GRENADA
TRINIDAD, TOBAGO
VENEZUELA
COLOMBIA
BR GUIANA
SURINAM
FR GUIANA
ECUADOR
PERU
BRAZIL
BOLIVIA
CHILE
ARGENTINA
PARAGUAY
URUGUAY
MALARIA NEVER PRESENT OR DIED OUT WITHOUT SPECIFIC ERADICATION MEASURES
MALARIA ERADICATED
ADVANCED, WITH ZONES WHERE ERADICATED
WITH TOTAL COVERAGE BEGUN
WITH PLAN OF OPERATIONS APPROVED, BUT WITH TOTAL COVERAGE NOT YET BEGUN
STILL WITHOUT PLAN OF OPERATIONS
JLV

Fig. 1

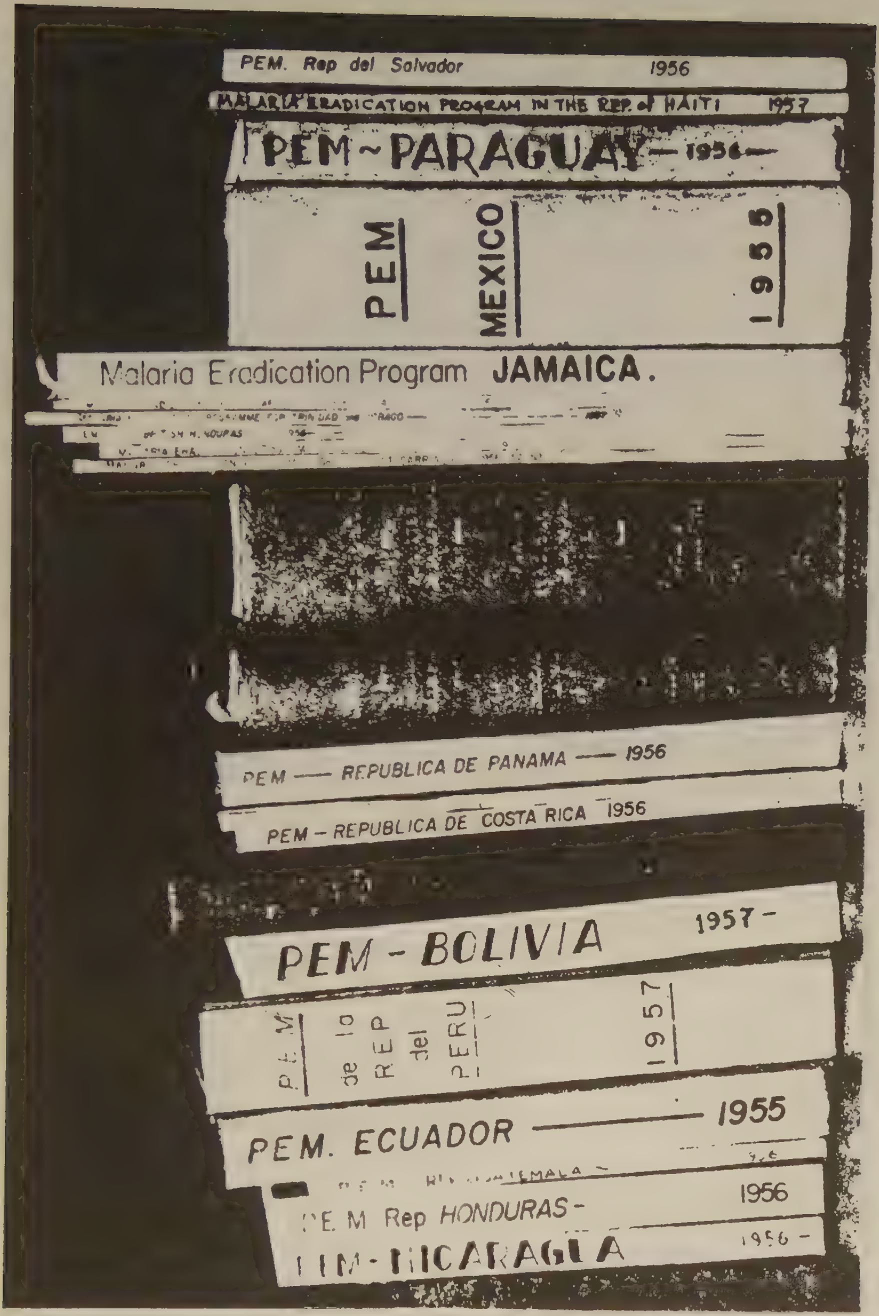
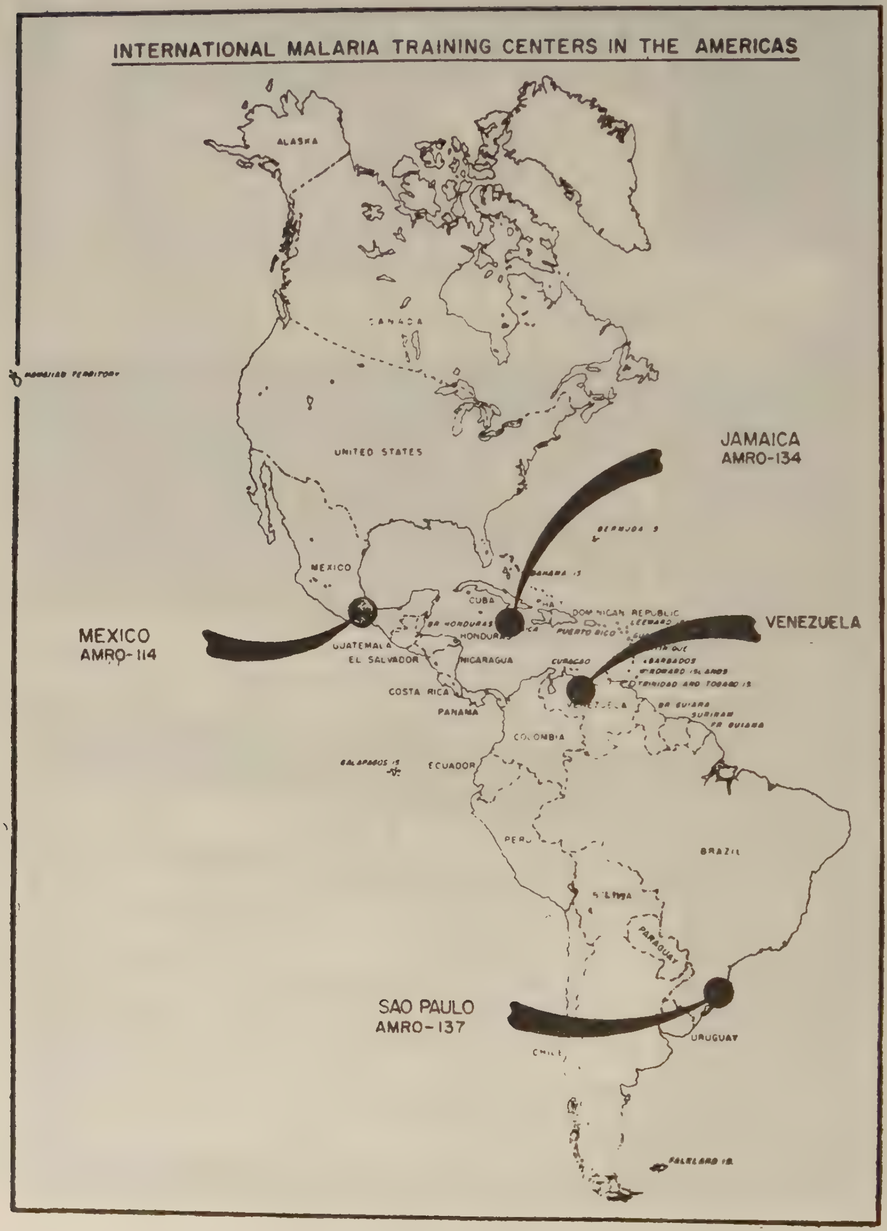

PEM. Rep del Salvador 1956
MALARIA ERADICATION PROGRAM IN THE REP. of HAITI 1957
PEM ~ PARAGUAY — 1956 —
PEM MEXICO 1955
Malaria Eradication Program JAMAICA.
PEM —— REPUBLICA DE PANAMA —— 1956
PEM – REPUBLICA DE COSTA RICA 1956
PEM - BOLIVIA 1957 -
P.E.M. de la REP del PERU 1957
PEM. ECUADOR 1955
P.E.M. Rep HONDURAS - 1956
1956 -

Fig. 1-*a*


INTERNATIONAL MALARIA TRAINING CENTERS IN THE AMERICAS
ALASKA
CANADA
HAWAIIAN TERRITORY
UNITED STATES
JAMAICA
AMRO-134
BERMUDA IS
MEXICO
BAHAMA IS
CUBA
HAITI
DOMINICAN REPUBLIC
LEEWARD IS
MEXICO
AMRO-114
BR HONDURAS
HONDURAS
PUERTO RICO
VENEZUELA
GUATEMALA
EL SALVADOR
NICARAGUA
CURACAO
BARBADOS
WINDWARD ISLANDS
TRINIDAD AND TOBAGO IS
COSTA RICA
PANAMA
VENEZUELA
BR GUIANA
SURINAM
FR GUIANA
COLOMBIA
GALAPAGOS IS
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PARAGUAY
SAO PAULO
AMRO-137
URUGUAY
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FALKLAND IS

Fig. 2

MALARIA ERADICATION IN GREECE

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I

The nation-wide antimalaria campaign of 1946-1949

Malaria transmission in Greece, according to all evidence, available, had been interrupted in all of the country, with but very few exceptions, by the end of 1949, that is, after a four years of intensive nation-wide antimalaria campaign (1).

This activity was mainly based on systematic house spraying with D. D. T. in all endemic rural areas of the country. Spraying was done once in a year, and the standard dose used was 1.80 g technical D. D. T. per sq. m. The average number of villages annually treated during the period 1946-1949 amounted to 5 047, and the protected population by this control method to 3 476 188.

Parallel to this work, larval control with D. D. T. was carried out in malarious urban areas, and in some cases peripheral house spray was also simultaneously applied. The preference given to larviciding in the case of urban areas was due to reasons of economy. The average annually protected urban population by larval control during the period 1946-1949 amounted to 1 443 881.

Thus, of the country's total population of approximately 8 million, 4 290 019, that is, the whole of the population exposed to risk, were protected over the years 1946-1949.

During the same period, an airspray program was carried out in some of the major swampy areas and rice fields, with chlorinated hydrocarbon insecticides.

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 483-502, 1959

No antimalaria method other than the above was used throughout the period under review.

The previous extensive epidemiological and entomological surveys of 1930-1937, conducted by the Malaria Department of the Athens School of Hygiene in cooperation with the Rockefeller Foundation Mission to Greece throughout the country (2) had provided valuable material for the planning of this nation wide campaign.

It was a fortunate thing that in the same period there was a well organized malaria control service available, whose scientific and technical personnel were experienced enough to adapt themselves to the requirements of the new techniques. The above services had been operating from 1937 within the organizational framework of the Athens School of Hygiene as an independent unit under the direction of the writer in his capacity as director of the Malaria Department of the School.

UNRRA, which arrived in Greece upon the liberation of the country (end of 1944), placed at our disposal, from the very outset, the necessary quantity of D. D. T. and other supplies to assist in carrying out the first field experiments (1945) in Greece with the newly discovered insecticide (3).

The results of these experiments were so encouraging in regard to the efficacy of the new insecticide, especially in rural surroundings, that no doubt was left about the favorable effect of an eventual expanded application of this insecticide (3, 4).

Meanwhile, valuable conclusions had been reached from the same insecticide applications regarding the house spray technique, which, as is known, was at that time in its early formative stage.

UNRRA subsequently furnished the Malaria Control Service with the necessary insecticides and other supplies for the first antimalaria drive.

So, in the spring of 1946, we were able to put into effect a thoroughly planned nation-wide malaria control program.

On the termination of UNRRA's activities in this country, ECA continued to provide the necessary material aid in the great antimalaria effort under way, and WHO, by its local representatives, followed the various phases of the work with keen interest throughout that period (5).

Assessment of results

At the end of the period 1946-1949, spleen rates of school children, which during the pre-D. D. T. era ranged in endemic areas from 25 % to 75 %, and in some cases reached as high as 100 % (2), dropped so much as to lose entirely their malariometric value and were therefore abandoned (1).

On the other hand, parasite rates of school children fell from 17,2 % (average for the period 1933-1939) to 1,7 % in 1946, 0,21 % in 1947, 0,15 % in 1948 and 0,15 % in 1949 (1).

In addition to the above data, the information gathered from all sources in the course of the antimalaria operations (malaria morbidity in the army, which at the time was in a state of mobilization, statistical data collected by dispensaries and civilian or military hospitals, reports by private practitioners, results of routine anopheline catches, consumption of antimalaria drugs, etc.) indicated that malaria incidence which in the pre-D. D. T. days was so high (1-2 million malaria cases annually) (2) had become quite insignificant (1).

Finally, the almost complete disappearance of *P. falciparum* and the nullification of the cumulative infant parasite rate for two successive years (1,24) were additional strong arguments in favour of the view that the interruption of malaria transmission in practically ali of the country was a fait accompli.

It might also be added that the obvious disappearance of even the indirect consequences of the endemy, the rapid expansion of rice cultivation, which so far had been under strict limitations on account of malaria, the growing activity of the rural population awakenning from the malaria torpor (1) — all this had a strong effect on public opinion and helped create the belief that malaria had virtually disappeared and consequently the evils that had befallen the country through this age-old scourge were coming to an end.

The government, sharing this optimistic view, proceeded about the end of 1949 to the consolidation with the other services of the Ministry of Hygiene of the special malaria control service — which, as previously stated, had been so far operating as an autonomous unit within the organization of the Athens School of Hygiene —, as it was felt that the reasons which originally made this measure necessary had ceased to exist.

II

Discontinuance of the residual spray program and organization of a system of epidemiological detection and surveillance (1950-1953)

Despite the highly favorable situation developed in Greece by the end of the 1946-1949 period, no one envisaged the possibility of relaxing or limiting the antimalaria measures under way, which, owing to their magnitude, bore heavily on the State Budget. And the Malaria Service, therefore, under its new dependent status, applied strictly, in 1950 also, the program of the previous 4-year period.

Malariologists, under the influence perhaps of the principles applied to antilarval campaigns, generally thought that residual spray programmes ought to be continued indefinitely. Before their eyes hung menacingly the specter of returning malaria (perhaps in a still more hideous form owing to the weakening immunity) as soon as spray work was, for one reason or another, discontinued.

In the light of these considerations, in no case was any thought given to the discontinuance of the residual spray programs.

Malariologists at that time were thinking in terms of malaria control. The idea of malaria eradication was closely associated with that of vector eradication, and no one did ever think that it would be possible to attempt to carry out malaria eradication in a wide area within a short period of time by merely mobilizing the means available.

However, early in 1951, certain conditions developed suddenly in Greece that made the continuance of malaria control programme problematic. Prices for insecticides on the world market, owing to the korean war, considerably rose, and this at a time when economic aid extended to Greece under the Marshall plan was coming to an end. Moreover, the production of insecticides and the existing stocks could not meet the substantially growing demand for them. Under these circumstances, the continuation of the Greek malaria control program was seriously threatened.

It was therefore considered advisable to place this vital problem under the consideration of an expert committee. This committee was composed of members of the American Mission Public Health Services in Greece, Prof. Parkinson, then on a special mission in Athens, Dr. Paul Russel, specially invited for this purpose, and the writer (6). The proposals of the administrative sources discussed at first by the committee were as follows: The reduction of the residual spray program ought to be of a general nature in all areas of the country and in the same proportion. The other proposal provided that the rate of reduction would be determined by the endemicity of each area as the main criterion. Finally, the Committee decided unanimously to accept our plan, which was based on an entirely different principle (6).

According to this plan (6), the house spray program would be continued, as before, with no restriction and to the extent the available quantity of insecticides permitted.

In the remaining country the house spray program would be entirely discontinued and in its place a system of epidemiological detection and surveillance, speedily organized, would be put into effect.

The purpose of this new organization would be to follow intensively and closely the course of malaria after the discontinuance of house spray, and to take immediate suppressive measures, wherever circunstances so required.

Malaria inspectors going from village to village under the program worked out for each area by the chief of the Malaria Service in each prefecture, would make house to house visits and take blood specimens of every potential malaria case. The same force would carry out the necessary search in the settlement involved (catches of adults and larvae) to evaluate conditions from an entomological point of view. The blood specimens collected would be forwarded to the mearest laboratory of the Malaria Service, and parasite positive cases would be placed as soon as possible by the same personnel under treatment and subsequently under observation for a certain period. If from the epidemiological and entomological data collected and the reports submitted by the inspecting force, active foci of malaria transmission were found to be present in a settlement, the whole area would immediately be given a suppressive house spray by utilizing for this purpose the sprayin means kept in readiness in the capital of each prefecture.

Responsible for the organization and operation of the new system in each prefecture would be the chief of the local malaria service. The regional malariologist on the other hand would carry out the general supervision of the malaria program under implementation in the pertinent district.

The plan provided also for all details of the set up of the new system, as well as for the exercise of control by the Malaria Headquarters. Special emphasis was placed in the plan on the progressive development and perfection of the epidemiological detection and surveillance system, and, especially, on the organization of new laboratory units. These were, as soon as established, to be forwarded to the most critical rural areas, so that the taking of the necessary suppressive measures should be made possible within the shortest space of time.

Areas excluded from the residual spray program would under the plan be the Island of Crete and Peloponnese with a total population of 1 570 026. It was found that these two areas presented the most suitable conditions for the implementation of the proposed experiment, while it was also estimated that the saving in insecticides resulting from the exclusion of these two areas from the spray program would be sufficient to offset the shortage created.

On the termination of the Committee's meetings, Dr. Paul Russel stated that he was extremely happy at the solution given to the matter, and expressed his complete satisfaction at the fact that the writer had accepted not only to work out the new program in its details, along the principles set forth, but also to undertake personally its implementation (6).

The eminent malariologist conceived immediately the importance of the unique occasion presented to carry out a wide field experiment that would probably provide the answer to a great many painful current questions.

At a subsequent meeting of the above Export Committee under the chairmanship of the Minister of Social Welfare and Hygiene, which was also attended by officers of the Ministry, a final decision was made to put the program prepared by the writer (7) into effect and thus in the early part of the 1951 malaria season the application of this program was started in the areas of Crete and Peloponnese. The abolished house spray was replaced in these areas by the epidemiological detection and surveillance program. In the remaining country, house spray was continued in 1951 as theretofore (8). As however it later evolved that the shortage of insecticides was greater than originally estimated it was found necessary to reduce residual spray in a certain proportion even in that section of the country.

Effect of the discontinuance of the residual spray program.

Malaria situation on the Island of Crete by the end of 1951, in spite of the complete abolition of residual spray program, looked highly satisfactory (8). Throughout the island no positive parasite case was detected in that year by the detection service (Table II) and no cause therefore appeared for the application of suppressive measures. In Peloponnese also, in the same year, there were only 40 parasite positives detected, and the cases where suppressive measures were indicated were very few (8). In addition, the annual malariometric indices in both areas remained entirely unaffected.

It was thus proved that the abolition of the house spray program in 1 600 villages — the average number usually sprayed in Crete and Peloponnese — did in no way affect the existing balance in those areas from the standpoint of malaria. And as the system of detection and surveillance, being applied by the existing personnel, involved no substantial additional expense, the saving effected in insecticides and labor days proved a real profit (8).

These encouraging results led to the decision to extend the system of detection and surveillance, applied in 1951 in Crete and Peloponnese, to the remaining areas of the country, which would also be excluded from the house spray program. The abolition of the residual spray program in Greece became thus general during the years 1952 and 1953 with the single exception of those villages where positive parasite cases had been detected in the previous year (8).

The total parasite positives detected throughout the country in 1952 and 1953 amounted to 408 and 1 403 respectively (Table III). The difference in the figures of those two years must be attributed to a large extent to the improvement made in the meantime in the system of epidemiological detection and surveillance that rapidly expanded all over the country.

Undoubtedly «Greece at no moment was completely malaria-free at the region echelon» (9) in the proper sense of the words. However, all available data show that by the end of 1949, malaria had become a rare disease in Greece. And it continued to be so during the immediately succeeding years also, as clearly reflected in the corresponding malariometric indices (24) and especially on the data of the epidemiological detection and surveillance system (Table II) organized in the meantime, which, owing to its greater responsiveness, made the control of the situation easier. And this favorable situation was maintained, in spite of the abolition of the residual spray program for three successive years in Crete and Peloponnese and for two successive years in the remaining country (8, 24).

It seems that the great scarsity of the almost total elimination of parasite carriers that followed the campaign of 1946-1949 played a decisive role in the maintenance of the above balance. It is also probable that the detection and treatment of parasite positive cases have contributed, in some measure to this effect.

Among the few positive parasite cases detected during the period 1951-1953, a part was certainly due to new infections. These infections, as is the case even to-day, originated in small and scattered foci of transmission all over the country, which represent the last escaped remnants of the great antimalaria campaign of 1946-1949. There is however no doubt that even these remnants would have long ago been eliminated, if the insecticides had not in the meantime become partly or wholly ineffective. A few selective sprayings, applied in the corresponding areas, would be quite sufficient to eliminate these last foci of infection.

The phenomenon of resistance, of which we gave early warning at the end of 1951 (18), naturally perplexed the situation and caused unavoidable delay in the complete elimination of malaria from the country (19, 20, 21, 22).

However, the observations made throughout that period in Greece were in many-ways instructive. Specifically, the following basically important conclusions were reached:

1) That by the systematic use of residual insecticides it is possible. under conditions corresponding to those prevailing in Greece, to obtain the interruption of malaria transmission within 3-4 years without the interference of other antimalaria methods (drugs, etc.).

2) That after the accomplishment of the above objective, the house spray program could harmlessly be abolished, but in order to

assure the results obtained it is necessary to organize in the corresponding areas a system of epidemiological detection and surveillance.

3) That the continuation of sprayings indefinitely, under conditions such as exist in Greece, is unnecessary and involves, besides a waste of money, the danger of development of resistance by local vectors, with final result the wearing out of a valuable antimalaria weapon.

The above remarks were placed under the consideration of the WHO Malaria Expert Committee convened in Istanbul in September 1953 (8) and subsequently reported in the periodic press.

Prof. Pampana, who followed closely the various phases of developments in Greece during that period, realized from the first moment the great importance of relevant conclusions, and in a pertinent study published in November 1954 in «Chronique de l'Organization Mondiale de la Santé» (10) makes, inter alia, the following statement: «Tirer la leçon de l'expérience faite en Grèce, c'est envisager un programme de lutte qui permettrait de renoncer aux pulvérisations avant que la résistance se développe.»

In a later article published in the same journal (11) the following comment is made: «Events in Greece have provided both a lesson and a warning: the maintenance of control inspite of interruption of spraying has shown that insecticide application may be stopped after some years without the reappearance of malaria; the development of resistance to chlorinated hydrocarbon insecticides in *A. sacharovi* has given a warning that the best weapon against malaria may lose its efficacy.»

All above observations were the prelude to the new orientations which, through the recommendations of Santiago (October 1954) and Baguio (November 1954) conferences were finally adopted by the historical resolution of the VIII World Health Assembly (May 1955). By this resolution it is declared that the final purpose of all efforts undertaken and of the new antimalaria strategy is the eradication of malaria from the world. This new strategy consists in launching an all-out attack on malaria areas as wide as possible by mobilizing and concentrating all available means together, so that malaria eradication from those areas might be accomplished within the shortest space of time and before vector resistance to the residual insecticides eventually develops (12, 13). The consolidation, on the other hand, of the results after the interruption of the spray program, and the elimination of the danger from possible escapes (remaining foci of transmission) is carried out by a program of epidemiological detection and surveillance (8, 14).

III

Antimalaria activities in Greece during the period 1954-1957

In the light of the problems created by the resistance of Greek vectors to chlorinated hydrocarbon insecticides, the Ministry of Hygiene appointed a special Malaria Committee, which, convening under the chairmanship of the Minister of Hygiene at the end of each year, takes notice of the work of the previous malaria season and formulates the malaria control program for the next year. Responsible for the implementation of this program is the Malaria Control Service of the Ministry of Hygiene. In addition, the members of the above Committee, in which the writer also participates, carry out at times inspections of the work performed by the Service.

The main points of the program carried out during the period 1954-1957, as worked out by the special Malaria Committee (17), are as follows:

1) *Application of preventive house sprays.* In 1954, the program of annual sprayings, suspended during the period 1951-1953, was again put into effect. The new house spray program, however, does not bear the expanded character of the period 1946-1949. As shown on Table I, the villages sprayed in the years 1954 and 1955 represent about 40 % only of these sprayed during 1946-1949. In the subsequent years, their number was reduced still further.

In selecting the villages in which preventive house sprays are to be applied, top priority is given to those that have presented positive parasite cases during the previous three-year period.

A substantial innovation of the new spray program is the introduction of several sprayings instead of a single annual one, — which aims at counteracting the vector resistance to the insecticides.

Another important innovation of the program is the periodic change in the insecticides used, both on the first spray and on the subsequent ones (D. D. T., Dieldrine, B. H. C., Chlordane).

Since vector resistance to the insecticides varies considerably from area to area, (20, 22) it was decided that in the future the choosing of insecticides for each area be governed, as far as possible, by the findings of the Busvine and Nash tests which recently are conducted in many areas in a systematic way (16).

It should be noted here that, owing to the generalized and obvious resistance of Greek vectors, particularly of *A. sacharovi,* to both groups of chlorinated insecticides, (20, 22, 27) serious doubts were repeatedly expressed even within the Committee as to the practicability of the preventive sprayings applied, and the danger was pointed out from a possible strengthening of that resistance (17, 52). The data of Table I

TABLE 1 — *Data of house spray program applied in Greece during the period 1954-1957* [1]

Years	House spray	
	Number of sprayed villages	Population of sprayed villages
1946-1949 (average)	5 047	3 426 186
1954	2 003	1 335 344
1955	2 017	1 325 398
1956	1 135	785 000
1957	1 327	948 409

TABLE 2 — *Parasite positive cases detected in Greece during the period 1951-1957* [1]

	Years						
	1951	1952	1953	1954	1955	1956	1957
Crete	0	2	2	6	6	1	3
Peloponnese	40	41	206	531	443	—	—
Remaining Greece	—	365	1 195	1 813	1 193	—	—
Whole Greece	—	408	1 403	2 350	1 642	680	1 445

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[1] Data of tables 1 and 2 were secured from the records of the School of Hygiene and the Malaria Service of the Ministry of Hygiene.

show that in the last years there is a clear tendency to reduce again the above sprayings.

2) *Application of suppressive house sprays.* These are applied according to the system established in 1951. The replacement of chlorinated hydrocarbon insecticides by organophosphorus compounds would in this case be desirable (22).

3) *Application of antilarval programs.* These are carried out mainly in urban areas. In view of the fact in the majority, if not the whole, of the urban areas malaria transmission had clearly been interrupted, the practicability of continuing many of the programs, at least from a malariological point of view was deemed doubtful (17, 25). Recently there is a tendency to reduce this part of the program also (16).

4) *Airspray.* After a great many efforts (17, 25), it was succeeded in 1957 in discarding this expensive method from the program in which it had been included early under entirely abnormal conditions. The psychological effect of this spectacular method on the population was so strong that any attempt to abolish it was met with stubborn reaction from various sides; and this, in spite of the fact that it had clearly been demonstrated that the airspray program, especially under the conditions it was carried out in Greece, offered no positive service and was perhaps detrimental as contributing to an accelerated and increased development of vector resistance (17, 24, 25). It would not perhaps be out of place to add here that in 1957, contrary to the fears expressed by the strenuous upholders of this method, no adverse effect whatsoever was observed as a result of the abolition of the airspray program; in fact there was an increase of 20 % in the rice cultivatiòn, according to information provided by the Malaria Service (16).

5) *Treatment of suspected malaria cases and of parasite positives.* To persons suspected of having malaria is now given, when taking the blood specimens, instead of the orginally used quinine, (1951) chloroquine base in a single dose of 600 mg for adults and a correspondingly smaller dose for children. In some areas, besides chloroquine, pyrimethamine was tried in single 50 mg doses with the object to prevent the development of gametocytes in the body of anophelines (16, 17). Cases that are found through laboratory examinations to be positive are placed under immediate treatment with chloroquine for a period of three days. This is followed by a 14 day sterilizing treatment with primaquine (15,

17). A good reason for the use of primaquine is the absolute prevalence of *P. vivax* in the positive cases detected.

6) *Mass sterilization positive cases.* This is mostly carried out in areas where there is a relatively higher number of positive cases. The primaquine used for the sterilization of these cases is dispensed to the patients directly by the malaria personnel throughout the 14-day period of treatment. This method was first practised in the spring of 1957 on a relatively large scale. Persons placed under sterilization amounted to 4 038 — all belonging to the category of positive parasite cases detected during the three-year period of 1954-1956 (16).

7) *Mass chemioprophylaxis.* This method also is preferably applied in areas with relatively higher residual malaria. For this purpose, pyrimethamine is used periodically (at 1-2 months' intervals). Mass chemioprophylaxis was first applied, on a relatively large scale, in 1957 (16).

8) *Epidemiological detection and surveillance.* It is more and more realized that, under the conditions that developed in Greece after the great antimalaria campaign of 1946-1949 and the building up of resistance by local vectors to the insecticides, the system of epidemiological detection and surveillance, which was initiated in 1951, constitutes the basis of antimalaria activity in this country (21). Intensive efforts are therefore being made to strengthen this important field by every means possible. Thus, in 1957 the parasitological laboratories of the malaria service were increased from 9 to 17. By this measure the time between the taking of the blood specimens and the reporting of the result to interested office will substantially be shortened, and in this way both the appropriate treatment and the application of suppressive measures will be more opportunely timed, and the whole system will become more efficient.

Efforts are also being made to arrange for the newly established 940 rural social security dispensaries to participate, as actively as possible, in the work of the epidemiological detection. Experience last year proved that these dispensaries are bound to play a primary role in the matter.

At the same time, various other measures are under consideration, which will help the effort being made, such as the active participation in detection work of municipalities and communities, schools, the army, out-patient clinics, especially in rural areas, private practitioners, private bacteriological laboratories, volunteer organizations, etc. (16). We are thus headings directly for that general mobilization of all forces, which we persistently appealed for since 1953 during the discussions of the special Malaria Committee and in our various publications (17, 21, 25).

IV

Present malaria situation in Greece

On the Island of Crete, in spite of the complete interruption of the spray program for seven successive years, the findings of the epidemiological detection and surveillance continued to be steadily negative. All of the very few positive parasite cases detected on the island (Table II) during that period were either relapses of old infections or had been imported from other areas. No new case of local infection was found throughout the above seven years. The three positive cases detected on the island in 1957 proved to have been imported from other areas (16). On the other hand, the surveys we made in recent years, to evaluate the actual distribution and density of vectors on the island, showed that in some cases the old breeding places of vectors have completely disappeared and in others breeding has clearly decreased, leaving on the island a perceptibly reduced anopheline density (anophelisme without malaria) (23).

Crete is therefore entitled to be included in the top priority list of countries or areas where complete eradication of malaria has been achieved. This favorable picture however does not suggest a weakening of the system of epidemiological detection and surveillance, particularly as the danger of parasites being imported from neighbouring infected areas is always imminent.

In the remaining areas of the country the number of positive cases detected during the last years remained steadily at low levels, with but very slight fluctuations (Table II). In 1957, a total of 1 445 positive parasite cases were detected. This number is higher than the corresponding one of last year, but is not very far from the number of positives detected in the immediately preceding years (Table II).

As the system of detection is increasingly expanded and improved, and has recently been strengthened, as already stated, by a wide network of rural social security dispensaries, it is only reasonable to conclude that escapes are constantly decreasing, and the number therefore of positives detected in 1957 is closer to reality that those of previous years.

The positive cases detected in 1957 are distributed among 37 of the 50 prefectures of the country, the other prefectures remaining completely negative. On the other hand, of the positives detected during that year, about 75 % belong to 6 prefectures (16). It is also to be noted that *P. falciparum*, which in the pre-D. D. T. period represented about 45 % of infections in Greece, has almost completely been eliminated. Moreover, the annual malariometric indices remain at the same low levels.

From all above facts, it is concluded that during the last nine years there have been no substantial changes in the Greek malaria situation, as developed by the end of 1949. The residual foci left by the great antimalaria campaign of 1946-1949 continued to be limited in number, extent and significance, and does not seem that any important new foci of transmission have developed in the meantime. On the contrary, it was recently observed that residual foci have tended to become localised and disappear. There is therefore many a good reason to believe that by the continuance of applied measures and, especialy, by the further development of the epidemiological detection and surveillance system, it will be possible to dispose of the difficulties that were caused by the vector resistance, and that, within a reasonable period of time malaria, will be definitively dislodged from its last strongholds in the country.

RÉSUMÉ

Cet article donne une description synthétique des différentes phases de la Campagne Antipaludique en Grèce depuis le début de l'introduction des insecticides chlorés dans ce pays (1954) jusqu'à ce jour.

Le travail est divisé en 4 chapitres:

Le chapitre I — Décrit brièvement la Campagne Antipaludique Nationale pendant la période 1946-1949, au cours de laquelle le D. D. T. fut seul utilisé, comme adulticide et accessoirement comme larvicide. Les données fournies montrent qu'à la fin de cette période la transmission du paludisme était pratiquement interrompue dans tout le pays.

Le chapitre II — Expose les tentatives faites dans la période suivante (1951--1953) pour suspendre le programme de «House Spraying» d'abord dans deux grandes régions, et ensuite dans le reste du pays. Simultanément est décrit, brièvement le système de surveillance épidémiologique, organisé en remplacement des traitements insecticides suspendus. Les résultats enregistrés au cours de l'exécution de ce vaste programme expérimental furent très satisfaisants, et ils ont beaucoup contribué à amener une révision des conceptions, alors en honneur, sur la stratégie antipaludique.

Cependant la résistance aux insecticides chlorés, développée par le principal vecteur local, à la même époque fut une source de difficultés nouvelles.

Le chapitre III — Relate les mesures prises dans la période consécutive de 1954-1957 pour écarter la menace, apparue à la suite du phénomène de résistance.

Le chapitre IV — Brosse un tableau de la situation actuelle du paludisme en Grèce. Il est confirmé que dans l'Ile de Crète, depuis plusieurs années, l'éradication du paludisme est un fait accompli et la situation peut y être définie comme «un anophelisme modéré sans paludisme».

Dans le reste du pays, la situation favorable obtenue à la fin de la Grande Campagne 1946-1949 n'a pas subi de grands changements pendant les 9 années consécutives, et ceci malgré les modifications radicales apportées au programme à diverses occasions, portant interruption partielle ou totale des aspersions et également malgré l'apparition d'une résistance aux insecticides chez le principal vecteur local.

Le nombre annuel des cas positifs détectés au cours de ces dernières années se situe à un niveau très bas et les foyers de transmission, ayant survécu à la Grande Campagne Antipaludique, continuent à être très limités en nombre, extension et importance. L'apparition des nouveaux foyers n'a pas été signalée et, au contraire, les anciens foyers de transmission ont tendance à diminuer et à se localiser.

De tous ces faits, l'auteur conclut que l'on peut logiquement espérer qu'avec la continuation des mesures, et notamment l'extension et l'intensification de la surveillance épidémiologique, il sera possible d'éliminer les conditions créées par la résistance du vecteur. Ainsi donc, dans des limites de temps raisonnable, l'éradication complète du paludisme serait obtenue dans la totalité du pays.

ABSTRACTS

In this paper a brief description is given of the various phases of antimalaria campaign in Greece from the original introduction and use of chlorinated insecticides (1945) to this day.

The work is divided into 4 chapters:

Chapter I — Contains a short review of the nation-wide antimalaria campaign of 1946-1949, which was exclusively carried out with D. D. T. This insec-

ticide was mainly used as an adulticide and, secondarily, as a larvicide. Data are further provided, which show that by the end of above period malaria transmission had been interrupted in practically all of the country.

Chapter II — Sets out the attempt made duringe the subsequent period of 1951-1953 to abolish residual spraying program, initially in 2 great areas and, later, in the remaining country as well. A brief description is further given of the system of epidemiological detection and surveillance organized to replace the spraying program abolished. The conclusions reached through this experiment were very satisfactory, and, when made known, contributed considerably to a revision of the concepts prevailing until that time on the antimalaria tactics. However, the resistance to insecticides, as developed by the main local vector, *A. sacharovi*, in about the same period, proved a source of further difficulties.

Chapter III — Deals with the measures applied during the immediately subsequent period of 1954-1957 to remove the menace which arose from the above cause.

Chapter IV — Reflects the present malaria situation in this country. It is stated that in Crete, since several years, a complete eradication of malaria has been achieved, and that the present situation in this island might be determined as «moderate anophelisme sine malaria».

In the remaining country the favorable condition developed on the termination of the great 1946-1949 antimalaria campaign showed no substantial changes throughout the subsequent nine-year period. And this, in spite of the stated radical revisions made, at various times, in the house spray program in the form of complete or partial interruption — and the resistance built up by the local vectores to the insecticides.

The annual number of positive cases detected in these last years, ranged at very low levels, and the foci of transmission left by the above campaign continued to be limited in number, extent and significance. It is further stated that no new important foci of transmission were observed; on the contrary, older foci have tended recently to decrease or become localized.

From all this, the writer concludes that there is many a good reason to believe that by the continuing measures, and, mostly, by further expanding the network of epidemiological detection and surveillance, it will be possible to eliminate the conditions created by the local vector resistance and that within reasonable time limits a complete eradication of malaria from the whole country will be accomplished.

SOMMARIO

Nel presente articolo l'autore descrive sinteticamente le diverse fasi della campagna antimalaria in Grecia, dalla introduzione degli insetticidi clorurati nel paese (1945) fino ai nostri giorni.

Livadas, G. A. — *Malaria eradication in Greece*

Il lavoro è diviso in 4 capitoli:

Nel capitolo I — Viene descrita brevemente la campagna nazionale antimalarica del periodo 1946-1949, la quale fu condotta esclusivamente con il D. D. T., utilizzato come adulticida e accessoriamente anche come larvicida. I dati forniti mostrano che alla fine di tale periodo, la trasmissione della malaria pratticamente era interrotta in tutto il paese.

Nel capitolo II — Viene esposto il tentativo fatto nel periodo successivo (1951-1953) di sospendere il programma delle aspersioni, da principio solo in due grandi regioni, e in seguito nel resto del paese. Conteporaneamente viene delineato il sistema di sorveglianza epidemiologica, organizzato in sostituzione delle abolite aspersioni. I risultati registrati nel corso di questo vasto esperimento furono molto soddisfacenti e contribuirono considerevolmente alla revisione delle concezioni che prevalevano in quel tempo nei riguardi della strategia antimalarica.

Ma la sopravenuta resistenza agli insetticidi clorurati nel vettore principale fu sorgente di nuove preoccupazioni.

Nel capitolo III — Vengono descritte le misure adottate nel periodo consecutivo (1954-1957) per affrontare la minaccia proveniente dall'apparizione del suriferito fenomeno.

Nel capitolo IV — Si dà una immagine della situazione odierna della malaria in Grecia. Viene confermato che nell'isola di Creta l'eradicazione della malaria è stata compiuta da parecchi anni. La situazione ivi può essere definita come «un anofelismo moderato senza malaria».

Nel resto del paese la situazione favorevole, come si presentava alla fine della grande campagna antimalarica del 1946-1949, non ha subito nei successivi nove anni dei notevoli mutamenti, e ciò, malgrado le modificazioni radicali apportate al programa, in diverse occasioni, nel senso di una parziale o totale sospensione delle aspersioni e malgrado l'apparizione del fenomeno della resistenza.

Il numero annuale dei casi positivi di malaria rivelati nel corso degli ultimi anni si trova costantemente a un livello molto basso e i focolai di trasmissione della malaria sopravissuti alla sudetta grande campagna, continuano ad essere limitati in numero, estensione e importanza. Non è stata segnalata l'apparizione di nuovi focolai di trasmissione e al contrario quegli antichi hanno la tendenza di localizzarsi oppure di scomparire.

Basandosi su questi dati l'autore conclude che si può logicamente sperare che con la continuazione delle misure in atto e specialmente con l'intensificazione e l'estensione del sistema di sorveglianza epidemiologica sarà possibile di eliminare le condizioni avverse create dalla resistenza del vettore. E cosi è d'attendersi che, nello spazio di tempo ragionevole, sarà ottenuta la completa eradicazione della malaria nella totalità del paese.

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MALARIA ERADICATION IN THAILAND

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INTRODUCTION

A quarter-century of organized malaria control in Thailand culminated in 1955 with the formulation of plans directed toward nation-wide malaria eradication. At this point the basic antimalaria organization and activities had been extended into the major malarious areas throughout the country, and the control effectiveness of residual house-spraying, supplemented by malaria treatment, had been thoroughly established. The development of the antimalaria program, including WHO/UNICEF assistance, 1949-51, and USOM assistance, 1951 to the present, has been treated in previous papers (Ayurakitkosol and Griffith, 1956, 1957).

In 1955 the ultimate objective of the USOM-assisted malaria project was restated more positively as eradication, rather than control. In this year Thailand was also one of the nations subscribing to the resolutions of the World Health Assembly toward world-wide malaria eradication. These important steps did not change the basic technical field activities.

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 503-530, 1959

but they gave impetus to reorganization and extension of the scheduled annual programs through the next several years.

The original concept of elimination of malaria in Thailand depended largely on the successful results obtained by the annual house-spraying campaign. Three or four years of spraying are usually sufficient to cause complete disappearance of the principal vector, *Anopheles minimus,* from routine adult and larval collections (Griffith, 1953). The correlative decline of malaria incidence has been strikingly rapid to a point of near extinction in numerous highly malarious areas. From these facts it was considered that house-spraying, accompanied by limited malaria treatment and vigilance against malaria introduction, would reduce the disease below a critical level necessary to its survival.

The malaria survey data of recent years have shown continued effectiveness of the house-spraying campaign, but have also revealed the necessity for increased emphasis on searching out and treating malaria cases. Both control evaluation and antimalaria vigilance in Thailand up to the present year have largely consisted of the comprehensive annual technical surveys, reaching every area of antimalaria operations and concentrating on villages with a malaria history or conditions conducive to a malaria hazard. The usual standard malariometric procedures have been followed, including both parasitological and entomological investigations, and antimalarial drugs have been administered to all suspected or proven malaria cases encountered by the survey teams. The inclusion or omission of any operational area in the annual house-spraying campaign has depended on the application of standard technical criteria to the annual survey data, as treated below in the discussion of survey and evaluation.

During the past three years, the survey results in areas after four or more years of operations have shown the percentages of population requiring protection by continued spraying to be 15.5 %, 25.1 % and 38.2 % in 1956, 1957 and 1958, respectively. In these same years, the percentages of population in vigilance areas requiring protection by resumed spraying have been 3.8 %, 6.3 % and 14.5 %, respectively. The prolongation and resumption ot spraying are believed due to population movements and other less evident epidemiological factors causing resurgence and redistribution of malaria in the absence of fully effective surveillance procedures. The Thailand malaria eradication program has recently been revised to provide for an intensive search for and treatment of malaria through house-to-house visits by antimalaria field units at bimonthly intervals in each cperational area, accompanying or following the house-spraying campaign.

The purpose of this paper is to present a review of the status of the antimalaria program in Thailand in 1958 and a description of the new plans for organization and procedures which have been established this year.

GENERAL CONSIDERATIONS

Thailand is an entirely tropical country of about 518,000 square kilometers and 22,000,000 population, bordered by Burma, Laos, Cambodia, the Gulf of Thailand, Malaya and the Andaman Sea. The major geographic regions may be distingued as the northern and western hills, the central plains, the northeastern plateau, and the southeastern and southern (peninsular) hills and coastal plains. There are three characteristic climatic seasons. with considerable annual and local variations. occurring most typically in the northerly areas: the summer (February-May), the rains (June-September) and the winter (October-January).

Malaria incidence has been highest in the northern hills, lowest in the central plains, but has occurred widely in all regions, with greatest prevalence in hilly areas where stream conditions are ideal for *Anopheles minimus*. This widely distributed species is thus far the only identified vector known to be effective in maintaining malaria in Thailand. There is recent evidence that. *A. leucosphyrus balabacensis* may be important in some localities in western, central and southeastern regions where it has been found infected. *A. sundaicus* was identified as a vector in the southern region 20 years ago, but has not been found infected since that time though common in coastal malarious areas. Both *Plasmodium falciparum* and *P. vivax* are prevalent, the former generally predominant, while *P. malariae* is rarely found. Transmission in most areas is greatest during the rains when malaria prevalence usually shows a peak, followed by a decline and a second peak during the winter.

During the five years preceding the first residual house-spraying in 1950, reported malaria deaths averaged over 45,000 annually (estimated as about 1 % or malaria cases) in a national population then approaching 18,000,000. The annual mortality rate which averaged around 250 per 100,000 in 1945-49 has declined since 1950 as follows (1957 estimated from preliminary reports):

Year	Malaria mortality	Rate per 100,000 population
1950	35,819	195.0
1951	34,225	183.4
1952	29,115	153.5
1953	21,451	111.4
1954	16,473	84.2
1955	14,520	73.1
1956	13,076	57.4
1957	10,439	47.5

Mortality statistics are accumulated routinely in government records in all districts, though the diagnosis must often be made by non-medical personnel. Morbidity records are available only from cases treated at health centers and hospitals; malaria is not a reportable disease in Thailand. The present antimalaria organization utilizes statistics from other sources as a general guide to malarious conditions, depending for technical guidance on annual malaria surveys conducted by malaria technicians. Such surveys have generally confirmed a high incidence of malaria throughout Thailand prior to control operations.

Most of the Thai people live in farming communities, the villages averaging about 100 houses (500 population), usually built near streams in groups of small wooden or bamboo cottages. Rice is by far the principal crop, though rubber, peas, coconut and sugar-cane are also major products. Less than 15% of the population is engaged in commerce, manufacturing, public services, fishing, mining and other occupations. Population movements are common and tend to complicate the problems of malaria hazards and protection of the people by residual house-spraying. The movements may be *permanent,* as by immigrants into new settlements, *seasonal,* as by farmers from village homes into field shelters in caring for their plantations, and *occasional,* as by migratory laborers, tourists and pilgrims.

An important step toward the international coordination necessary for malaria eradication in Southeast Asia was made in 1956 with the formation of the Antimalaria Coordination Board. The members of this board including representatives of Burma, Cambodia, Laos, Malaya, Thailand and Vietnam, hold annual meetings (attended also by representatives of WHO, USOM and other interested agencies) to exchange information and consider mutual problems of their antimalaria programs. Thailand has also had a coordination conference with Burma in 1956, especially concerned with malaria problems along their common border, and has cooperated closely with Laos since 1956 in technical training and advisory services toward malaria eradication.

The antimalaria program in Thailand includes the basically required activities of organization and implementation, training of personnel, surveys for guidance and evaluation, residual house-spraying against malaria vectors, treatment of malaria cases, public information on antimalaria measures, and vigilance against the return of malaria. These activities are all necessarily large-scale and complex, and a full treatment is beyond the scope of this paper which will concentrate on latest developments. Reference may be made to previous publications for further details (Ayurakitkosol and Griffith, 1957; Griffith, Thurman and Butler, 1957; Thurman, 1954).

ANTIMALARIA ORGANIZATION

The malaria eradication program in Thailand is conducted by the Division of Malaria and Filariasis Control, Department of Health, Ministry of Public Health. This organization was founded as a section in the Division of Communicable Disease Control in 1934 and was given Division status in 1943. The present intensive antimalaria campaign is operated as a special eradication project with advisory, training and financial assistance from USOM. The staff of the Division in June 1958 included 509 members on year-round duty: 14 medical officers, 7 non--medical officers, 51 first class and 165 second class technical assistants, 107 technical aides and 165 auxiliary personnel. Two technical advisers were assigned by USOM to the Malaria Eradication Project.

The major headquarters of the antimalaria operations of the Division include the Central Office at Bangkok, four Regional Offices (Northern, Northeastern, Central and Southern) directly responsible to the Central Office, and five Subregional Offices (two Northern and three Central) directly responsible to their respective Regional Offices. Each of the major headquarters has a resident staff, including at least one officer and a variable number of technical assistants; office, laboratory and warehouse buildings and facilities, and assigned equipment and supplies; an approved depository for allotted funds; and jurisdiction over a number of the provincial areas which are operated from the headquarters and 30 field stations. Operations are now being conducted in 61 (of 71) provinces, directly protecting over 12,000,000 population.

In addition to the administrative headquarters detailed above, there are two new laboratory and training centers under construction at Chiengmai and Phrabuddhabat. These provide offices, libraries, laboratories, insectaries, and quarters for resident personnel and students. The centers are expected to serve both the present malaria eradication program and a later development of investigation and control of vector--borne diseases in general. The training program includes special courses for a large number of students from Laos, Vietnam, Indonesia and other countries, in addition to the regular and refresher courses for Thai malaria technicians.

New organizational unit plan. A revision of the basic plan of personnel units is believed essential to the intensification of the antimalaria campaign required for the success of the malaria eradication program. Then new plan provides a *field unit* of one technical assistant and four technical aides for each area of about 100 villages (50,000 population), a *laboratory unit* of one technical assistant and one technical aide for each five field units, and a *headquarters unit* of one officer and one technical assistant for each four laboratory units (which will also usually work out of the headquarters). The estimated personnel requirements according to this plan may be summarized as follows for each 1,000,000 population in the operational areas:

Organizational unit	No. units	Pop. per unit	Total personnel		
			Officer	Assist.	Aide
Headquarters Unit	1	1,000,000	1	1	
Laboratory Units	4	250,000		4	4
Field Units	20	50,000		20	80

In this new organizational plan, each field unit will perform any of the routine field activities required in the area to which the unit is assigned. If *house-spraying* is required, the technical assistant will serve as the supervisor and the four technical aides will serve as foremen, with three spraymen and one porter-mixter employed locally for each foreman during the spraying campaign. If *surveys* are being conducted, the field unit will do entomological investigations, spleen examination, blood film collection, malaria treatment and public information, as during previous years (except that the blood slides will be examined by the laboratory unit, rather than the field unit). If *surveillance* is instituted, the field unit will discontinued all malariometric survey activities and concentrate on a house-to-house search for fever cases, treatment with antimalarial drugs, blood film collection (for examination by the laboratory unit) and public information. The details of survey and surveillance plans and procedures are discussed below.

A minimum number of officers and assistants will also be required for the Central and Regional Offices and the two laboratory and training centers at Chiengmai and Phrabuddhabat. The technical personnel requirements for a malaria eradication program operating in areas of about 12,000,000 population may therefore be estimated as follows:

Assignment	Officer	Assist.	Aide	Total
Central office	2	2		4
Regional offices	4	4		8
Laboratory and training centers	2	8		10
Operational areas:				
Headquarters units	12	12		24
Laboratory units		48	48	96
Field units		240	960	1,200
Total required	20	314	1,008	1,342
On duty June 1958	21	216	107	344

The technical personnel on duty in June 1958 was far short of the number required for the new organizational plan; however, it will be noted that the greatest demand could be met by the addition of technical aides. These may be quickly employed without the competitive examination required for permanent Civil Service status. They are readily recruited from candidates with the equivalent of high school education and can be put on duty with relatively short training for their specific tasks. The steps toward putting the organizational plan into operation have also included the opening of a new training course for additional technical assistants and short refresher courses for assistants already employed.

With the adoption of the new plan in a malaria eradication conference in Bangkok in June 1958, it was recognized that it could not be instituted immediately throughout all operational areas in Thailand. It could only be decided to proceed as rapidly as possible toward complete coverage in accordance with the plan, with the expectation of reaching most of the malarious areas by the close of the year. Priorities were necessarily established to assure a logical development, with respect to the most immediate requirements in advancing malaria eradication. These priorities were as follows for the last half of the year:

(1) Surveys in areas of active house-spraying in 1958 up to third year of spraying. (Surveys will be discontinued in favor of surveillance in all areas after the fourth spraying, as discussed under surveys and surveillance below.) The post-spray surveys are essential to determine the extent of the 1959 continuing house-spraying campaign.

(2) Surveillance in the present vigilance areas, taking the oldest areas first and working back as far as possible toward complete coverage up to the areas in the fourth year of operations.

(3) Surveillance in the areas where spraying has been resumed after a period of vigilance.

(4) Surveillance in the areas newly placed under vigilance in 1958, having met the criteria for interrupting house-spraying in the 1957 surveys, following one to three years of consecutive annual spraying campaigns.

HOUSE-SPRAYING CAMPAIGN

The principal antimalaria activity in Thailand is the residual house--spraying campaign, scheduled mainly during the dry season in the first half of each year. The objective is to spray all houses in each operational area once yearly for a number of years (usually three to four) determined b the results shown in the annual technical surveys. (See criteria below in the discussion of surveys). The homes of over 12,000,000 people have been sprayed once to several times each since 1950, and spraying has been discontinued in favor of vigilance in areas of over 4,500,000 population. The progress of the campaign may be tabulated as follows:

Year	Project agencies	Population protected		
		Spraying	Vigilance	Total
1950	TG/WHO/UNICEF	77,503		77,503
1951	TG/WHO/UNICEF/USOM	581,312		581,312
1952	TG/USOM	1,570,249		1,570,249
1953	»	3,016,808	63,727	3,080,535
1954	»	4,266,442	414,776	4,681,218
1955	»	5,618,856	1.636,192	7,255,048
1956	»	7,364,176	3,052,107	10,416,283
1957	»	7,640,891	4,383,810	12,024,701

The house-spraying work is done by a basic operational unit consisting of a supervisor and four spraying squads, each squad being made up of a foreman, three spraymen and a porter-mixer. In accordance with the organizational plan discussed above, the technical assistant and four technical aides of the field unit act as supervisor and foremen, while the spraymen and porter-mixers are locally employed during the annual spraying campaign. Averaging 10 houses per sprayman-day, the field unit can complete a total spraying of its assigned area of 100 villages (10,000 houses, 50,000 population) in about 90 working-days. It is expected that the new plans of survey and surveillance will search out malaria foci, so that spraying can be limited to critical locations.

Both D. D. T. and dieldrin are utilized in Thailand, mostly as 75 % water-dispersible powder which is mixed with water at the site of spraying. The insecticidal suspension is applied with hand-operated ais compression sprayers delivering a fan-spray to interior house-walls and low ceilings at nominal rates of 2.0 gm/m^2 100 % D. D. T. and 0.25 gm or 50 gm/m^2 100 % dieldrin. (The lower dosage of dieldrin has been used only in the Northeastern Region and is being abandoned in favor of the higher dosage for greater effectiveness.) The residual house-spraying campaign in Thailand in 1957 — data from the 1958 campaign being incomplete at the time of this writing-is summarized in Table I.

TABLE 1 — *Antimalaria house-spraying campaign in Thailand in 1957*

Spraying Data	DDT 100 % 2.0 gm/m^2	Dldn 100 % 0.25 gm/m^2	Dldn 100 % 0.50 gm/m^2
Villages sprayed	13,247	1,872	92
Houses sprayed	1,236,617	178,245	11,403
Occupants of houses	6,546,773	1,035,777	58,341
Insecticide (kgm 100 %)	229,442	5,391	757
Sprayman-days	132,744	23,352	1,110
Surface sprayed (m^2)	103,890,997	19,594,654	1,263,942
Land area (km^2)	234,644	35,881	1,355
Houses per village	93.4	95.2	124.0
Population per village	494.2	553.3	634.1
Houses per km^2	5.3	5.0	8.4
Population per km^2	27.9	28.9	43.1
Occupants per house	5.3	5.8	5.1
M^2 per house	84.0	109.9	110.8
Houses per sprayman-day	9.3	7.6	10.3
M^2 per sprayman-day	782.6	839.1	1,138.7
Gm. 100 % ins. per house	185.5	30.2	66.4
Gm. 100 % ins. per m^2	2.21	0.28	0.60
Gm. 100 % ins. per capita	35.05	5.20	12.98

SURVEY AND EVALUATION

The routine technical surveys are conducted by the field units in their assigned areas, mainly during the rains and cool season in the last half of each year which is the most favorable period for malaria transmission and prevalence. The surveys are distributed in accordance with a modified random sampling method, with the objective of reaching every canton (administrative group of villages) and at least 20 % of all villages in the operational areas. In the selection of the villages to be surveyed, priority is given to those where malaria has been most prevalent or where conditions appear most conducive to a malarious situation. The routine survey procedures of the field unit include the following:

(1) House collection and identification of adult anophelines.
(2) Stream collection and identification of immature anophelines.

(3) Dissection of adult female anophelines for cocysts and sporozoites.

(4) Blood film collection from infants (aged 1-11 months) and children (aged 2-9 years), the slides to be examined by the laboratory unit.

(5) Spleen examination of children (aged 2-9 years).

(6) Treatment of suspected malaria cases with antimalarial drugs.

(7) Public information on malaria and antimalaria measures, especially directed toward promotion of public understanding and cooperation.

(8) Maintenance of field records (to be submitted with the blood slides to the laboratory unit). The routine survey accomplishments in 1957 are summarized in Table II.

In past years the field units have also examined the blood slides and assembled the field records on standard summary sheets, but the new organizational plan assigns these duties to the laboratory units. This is a move directed toward increased efficiency in identification of malaria parasites and handling of records for rapid technical analysis. The laboratory units work in the headquarters and field stations, servicing both survey and surveillance activities by the field units. The new plan is expected to provide time for a more thorough coverage by the field units in their routine survey activities. The laboratory units will also participate in special studies which may be needed in various localities, leaving the field units to concentrate on the routine survey and surveillance requirements in their assigned areas.

Evaluative analysis. The survey data are analyzed prior to each annual house-spraying campaign to determine the inclusion or omission of each surveyed canton (the basic operational unit for survey and spraying). The standard criteria applied in Thailand in making this determination have been treated in detail in previous publications (Ayurakitkosol and Griffith, 1956, 1957). In summary the criteria require that the routine surveys show no *Anopheles minimus* or other proven vector, no malaria infected infants (aged 1-11 months), a malaria parasite rate of less than 1 % and a spleen rate of less than 10 % in children (aged 2-9 years), and no significant hazard of malaria resurgence or introduction.

When the criteria are met in a canton, it is omitted from the next house-spraying campaign, irrespective of the number of years of anti-

TABLE 2 — *Routine malaria surveys in Thailand in 1957*

Survey Data	Unsprayed areas	Sprayed areas	Vigilance areas	Resprayed areas	Total
Villages visited	345	2,393	1,197	119	4,054
Houses in villages	43,709	229,462	139,575	13,626	426,372
Population in villages	244,024	1,200,942	704,358	60,560	2,209,884
Houses inspected	8,419	33,306	19,351	1,949	63,025
With *A. minimus*	49	253	30	20	352
Infestation rate	0.58 %	0.76 %	0.16 %	1.03 %	0.56 %
Dips in aquatic habitats	64,050	275,830	156,405	18,100	514,385
A. minimus found	135	587	53	101	876
Average per 100 dips	0.21	0.21	0.03	0.56	0.17
Anopheles dissected (all neg.)	2,308	15,794	6,092	1,056	25,250
Infants (aged 1-11 months)	3,343	26,534	14,594	1,274	45,745
Malaria infected	36	89	25	5	155
Infant parasite rate	1.08 %	0.34 %	0.17 %	0.39 %	0.34 %
Children (aged 2-9 yrs.)					
Blood examination	11,539	63,710	25,489	3,836	104,574
Malaria infected	271	1,947	385	66	2,669
Child parasite rate	2.35 %	3.06 %	1.51 %	1.72 %	2.55 %
Spleen examination	27,803	161,802	84,367	9,497	283,469
With splenomegaly	1,895	17,357	2,636	728	22,616
Child spleen rate	6.82 %	10.73 %	3.12 %	7.67 %	7.98 %
Fever cases treated	4,564	43,276	25,074	2,689	75,603
Population affected	1.87 %	3.60 %	3.56 %	4.44 %	3.42 %

NOTE — The above data are illustrative of the volume of work required by the surveys and the generally low level of malaria prevailing throughout the country in areas selected as most likely to be malarious. The areas remaining unsprayed are those with relatively low initial malaria endemicity.

malaria operations in the canton. This is made possible by safeguards against premature withdrawal of spraying, both in the criterion on the absence of a proven vector (a unique feature in Thailand) and by provision for immediate institution of surveillance. The new organizational plan provides in every area a field unit which can flexibly conduct any of the required operations — spraying, survey, surveillance, or respraying (after institution of surveillance) — as may be required.

The results of application of the standard criteria to the 1957 survey data in planning the 1958 house-spraying campaign are shown in Table III. Up to the present year antimalaria vigilance has been conducted in areas where house-spraying has been discontinued, utilizing the same procedures as for the routine surveys (except in relatively limited experimental areas discussed below). It will be noted that Table III shows a marked decline of the house-spraying requirement year by year in the areas continuously sprayed, but resumption of spraying is required in vigilance areas of 744,738 population. This is 6.3 % of the total population protected and 10.1 % of the 1958 house--spraying campaign. Spraying has also been prolonged beyond four years in areas with a population totalling 785,598 or 10.2 % of the 1958 campaign.

The routine survey procedures are now recognized in Thailand as too insensitive to be of practical value in exposing malaria foci in vigilance areas or in areas which have had several years of intensive house-spraying. It is believed that both resumed and prolonged spraying can be largely eliminated by institution of an adequate surveillance program in each operational area after the first few years of insecticide application. Accordingly the routine surveys will be limited from 1958 onward to pre-control surveys in new areas or post-control surveys in areas which have had no more than three consecutive years of spraying.

If a canton requires a fourth year of spraying on the basis of the standard criteria applied to the survey results of the third year, surveillance will be instituted in the last half of the fourth year following the spraying campaign. The usual malariolometric procedures will then be abandoned and the activities of the field unit will be devoted to an intensive search for malaria — village by village, house by house — in accordance with the surveillance procedures discussed below.

TABLE 3 — *Population to be protected in Thailand in 1958 based on 1957 malaria surveys*

Year control began	Population protected								
	Regular spraying campaign	%	Resprayed following vigilance	%	Total in areas of spraying	%	Vigilance following spraying	%	Total in controlled areas
1958	245,006				245,006				245,006
1957	742,797	94.1			742,797	94.1	46,833	5.9	789,630
1956	2,532,159	84.8	143,088	4.8	2,675,247	89.6	311,109	10.4	2,986,356
1955	1,830,878	65.7	116,217	4.2	1,947,095	69.9	838,718	30.1	2,785,813
1954	769,589	44.7	226,390	13.2	995,979	57.9	725,602	42.1	1,721,581
1953	504,731	28.9	184,126	10.5	688,857	39.4	1,059,205	60.6	1,748,062
1952	193,466	17.3	67,710	6.1	261,176	23.4	857,159	76.6	1,118,335
1951	53,549	7.4	4,762	0.6	58,311	8.0	666,885	92.0	725,196
1950	33,852	30.1	32,445	28.8	66,297	58.9	46,360	41.2	112,657
Total......	6,906,027	56.5	774,738	6.3	7,680,765	62.8	4,551,871	37.2	12,232,636

NOTE — The percentages of population protected by continued spraying, respraying and vigilance in areas in which control began in 1950 are not truly representative of the control effects of eight years (1950-57). All of the population protected by the regular spraying campaign is located in an area affected by influx of settlers and expansion of housing, and the houses consequently vary in the number of years sprayed. All of the population protected by respraying following vigilance is located in one district where evidence of malaria transmission (in 6 villages) was followed by respraying of the entire district (82 villages). This was done, rather than a limited spraying concentrated on the indicated malaria foci, to provide increased protection against possible malaria resurgence in the general area.

SURVEILLANCE

In the Sixth Report of the Expert Committee on Malaria (1956) it is pointed out that adequate surveillance is essential to malaria eradication and is that part of an antimalaria program which distinguishes the objective as eradication rather than control. The basic surveillance procedures are principally directed toward searching out and treating malaria cases, with attention to discovering and eliminating sources and foci of malaria. A special surveillance organization is required to make a regular cycle of contacts with every household in each operational area at stated intervals during the year. This intensive seaching process is the key to effective surveillance, though it may be supplemented advantageously by obtaining the cooperation of hospitals, health offices and other agencies in notification of malaria.

To provide the necessary basic information on the «visiting capacity» of a field unit, as well as other foundation material for the surveillance process, experimental village by village, house by house visits were conducted in large vigilance areas in northern Thailand from mid-1957 to mid-1958. A part of the results significant to planning may be summarized as follows:

Data	Aug.-Dec.	Feb.-June	Total
Villages visited	461	545	1,006
Houses visited	57,174	62,324	119,498
Visiting man-days	2,240	2,318	4,558
Man-days per village	4.9	4.3	4.5
Houses per man-day	25.5	26.9	26.2
Infants (all examined)	7,817	12,511	20,328
Malaria positive infants	3	9	12
% » »	0.04	0.07	0.06
All other population	283,136	287,746	570,882
Population with fever	2,581	8,770	11,351
% » »	0.91	3.05	1.99
Malaria positive cases	6	42	48
% » »	0.23	0.48	0.42

The data tabulated above were collected by field teams of varying composition in technical assistants and aides, working linearly across the experimental area, generally without repeating visits to the same locations. The data would indicate that a five-man team could be expected to visit over one village daily and over 25 houses per man-day. This would establish a quarterly cycle for a field unit conducting surveillance in an area of 50,000 population $\left(\frac{50{,}000 \text{ population}}{5 \text{ men} \times 25 \text{ houses}} = 80 \text{ working days} \right)$. However, the experimental field teams were trying a new type of program in areas not made familiar by repeated visits, and they were also performing more time-consuming duties than will be required of the field units in the new organizational plan.

The experimental work, for example, included blood film collection from all infants, blood slide examination, completion of diagnostic and epidemiological forms, and entomological investigations. The field units are now following simplified surveillance procedures as discussed below; the headquarters and laboratory units will take care of other requirements. The saving of time thus effected can be expected to increase the field unit «visiting capacity» at least by half again, thus making feasible a bimonthly cycle of repeated visits to every village and house in the assigned area.

The malaria findings shown in the above tabulation of experimental data indicate an extremely low persistence of malaria in the vigilance areas covered. This is especially remarkable when it is considered that these areas have been protected for a variable number of years chiefly by annual technical surveys and treatment of malaria cases encountered. The findings are encouraging in showing that the disease has been controlled almost to nil, but they are also illustrative of the urgent requirement to find and eliminate the last remnants of the malaria reservoir while it is at prolonged low ebb. The malaria positive infants indicate the constant danger of a persistent malaria transmission hazard at some points in the vigilance areas.

New operational plan. The standardized provisions and procedures for surveillance now being put into effect in Thailand include the following major points:

(1) Surveillance will be instituted in each canton as soon as the criteria for interrupting house-spraying are met in any of the first three years of spraying; however, if the criteria are not met after the third annual spraying, surveillance will begin in the last half of the next year, following the fourth spraying, and the routine technical surveys will be discontinued.

(2) Once surveillance has been established in a canton, the routine technical surveys will not be resumed, even though the surveillance results may cause house-spraying to be continued or resumed in all or part of that canton.

(3) The criteria for continued or resumed spraying after surveillance has been established will be limited to evidences of indigenous malaria and active malaria transmission. Imported or sporadic malaria in the absence of evidences of transmission will not be sufficient justification for spraying.

(4) Spraying after surveillance has been established will be limited as a rule to the village in which evidences of indigenous malaria and active malaria transmission have been found, though neighboring villages may be included, if critically involved in the indicated malaria hazard.

(5) Surveillance will be conducted as a year-round program, except that in villages requiring spraying on the basis of surveillance results, the surveillance may be interrupted during the spraying operations, if necessary.

(6) The visits to villages and houses will proceed in a bimonthly cycle in accordance with a schedule to be established for each area. Places which are impossible to reach during a cycle, due to flood or other good reason, will be omitted after a reasonable trial and visited in the next cycle.

(7) The surveillance will be done by the field units of one technical assistant and four technical aides, visiting each house in a cycle of about 100 villages (50,000 population) per unit at intervals of about 60 days and performing the following duties:

a) Blood film collection from all present or recent fever cases, the slides to be examined by the laboratory unit.

b) Single dose treatment with chloroquine and pyrimethamine antimalarial drugs of all present or recent fever cases, the two drugs to be given together and immediately to each case, in accordance with the following dosages:

Drug (dosage in mg base)	Over 12 years	6-12 years	3-6 years	1-3 years	Under 1 year
Chloroquine	600	450	300	225	75-100
Pyrimethamine	100	50	25	25	None

c) Completion (except blood slide examination) of a record of surveillance activities (Fig. 1) at each village and submission of the records and accompanying blood slides to the laboratory units.

d) Information to the public on malaria, the antimalaria program, and the protection of home and village against malaria.

(8) The laboratory units of one technical assistant and one technical aide for each five field units will perform the following duties in connection with the surveillance program:

a) Blood slide examination and completion of each village record of surveillance by adding the laboratory findings for each fever case reported. (The card shown in Fig. 1 provides columns to check regative or parasite species. The presence of gametocytes is shown by a check in column G and a circle around the check in the appropriate species column or columns.)

b) Compilation of a summary record for each canton from the village surveillance records.

c) Assistance with epidemiological investigations, as directed and supervised by the headquarters unit.

(9) The headquarters units of one officer and one technical assistant for each four laboratory units and 20 field units, with further assistance by clerical, mechanical and other auxiliary personnel, will have the following over-all functions:

a) General administration of all field activities, including direction of the program, recruiting and training of personnel, issuance of equipment and supplies, maintenance of records and similar duties, with direct responsibility to the Regional Office concerned.

b) Epidemiological investigations of proved malaria cases and follow-up of persistent *vivax* and *malariae* cases, as may be necessary.

c) Coordination with other health agencies, investigations of problem areas, and similar special requirements.

Cooperative assistance. An effective program of surveillance demands the concentration of specialized personnel on the necessary objectives and procedures, thus usually requiring that the program be conducted by the antimalaria organization under centralized direction, without essential dependence on any other organization. However, the searching out and treatment of malaria cases can be greatly assisted by the cooperation of various agencies.

In Thailand 70 provincial hospitals and 750 health centers distributed in every province treat numerous cases diagnosed as malaria. Further development of plans and facilities is needed for confirmation of suspected malaria by blood examination and notification to antimalaria headquarters of confirmed cases and places of origin to anable epidemiological investigation. Several thousand «canton doctors» (indigenous healers) and equally large numbers of mid-wives are government-sponsored throughout the country. Their cooperation, while presenting obvious difficulties in organization, supervision and reporting, could serve in indicating possible foci of malaria.

The armed services maintain numerous hospitals and posts which should be sources of information on areas regarded as malarious. Compulsory education in Thailand brings the highly malaria-susceptible childhood group into a school system which should be adaptable for routine reporting of health conditions among children. Highway and railway organizations, resources development authorities, agricultural settlements, and other agencies maintain a variety of operational units which could be helpful in measures for exposure of malarious conditions, prompt treatment of malaria cases, and prevention of redistribution of malaria.

A promising plan has been developed with the cooperation of the Department of Public Welfare for a special surveillance program in agricultural settlements. The procedures now under field trial potentially affect a population exceeding 100,000 in numerous self-help settlements sponsored by the government for low-income groups in various parts of the country.

The plan depends essentially on the organization of the self-help settlements which divides the areas into sections, each having a quota of households and a section leader elected by the householders. Since the section leader is required to visit every house at frequent intervals, a mechanism is readily available for the finding of fever cases. It is also stipulated in the plan that all householders should cooperate in seeking immediate examination and treatment at the hospital, health unit, or malaria unit in the community, if a fever case develops. The malaria unit is charged with responsibility for coordinating the health services of the area, blood examination and epidemiological investigation of proved malaria cases.

While the plan is recognizably applicable only to a relatively limited part of the national surveillance program, it has importance in providing added protection to groups peculiarly vulnerable to such problems as exposure to malaria vectors in newly cleared areas, introduction of malaria by infected immigrants, and the movement of completely non-immune settlers into areas of undetermined malaria hazard.

SCHEDULE FOR FUTURE YEARS

It is expected that the house-spraying campaign requirements can be reduced annually at a rate of not less than areas of 1,500,000 population. The percentages of population requiring protection by spraying in the 1958 program, after various years of control, support this expectation when applied to the population to be protected in future years. It may also be noted that the 1958 spraying requirements include prolonged continuous spraying and resumption of spraying in vigilance areas which the institution of adequate surveillance should make unnecessary. A theoretical projection of the house-spraying campaign and other operational requirements may be seen in Table IV.

In this projection the annual spraying estimate includes both those areas which will still remain in the general campaign evaluated by technical surveys and other areas in which surveillance will ilmit the spraying to malaria foci. As the spraying requirement is reduced, the

TABLE 4 — *Projection of malaria eradication program in Thailand 1959-65*

Program elements	1959	1960	(All figures in thousands)			1964	1965
			1961	1962	1963		
Population protected							
Major areas							
House-spraying	6,000	4,500	3,000	1,500			
Surveillance only	6,000	7,500	4,500	4,500	4,500	3,000	1,500
Completed program			4,500	6,000	7,500	9,000	10,500
Minor area							
Reconnaissance			4,500	1,500	1,500	1,500	1,500
Completed program				4,500	6,000	7,500	9,000
Total							
Active program	12,000	12,000	12,000	7,500	6,000	4,500	3,000
Completed program			4,500	10,500	13,500	16,500	19,500
Financing							
USOM ($)							
Training abroad	10	10					
Advisory services	30	30	30	30			
Commodities	225	275	175	25			
Total	265	315	215	55			
Thai Government ($)							
House-spraying (field costs)	7,200	5,400	3,600	1,800			
Surveillance only (field costs)	4,800	6,000	3,600	3,600	3,600	2,400	1,200
Reconnaissance (field costs)			3,600	1,200	1,200	1,200	1,200
Centralized funding	2,800	2,700	1,700	1,300	900	800	600
Vector centers	200	200	300	300	300	600	1,000
Total							
Regular Budget	5,000	6,000	6,000	6,000	6,000	5,000	4,000
Counterpart Funds	10,000	8,300	6,800	2,200			
Grand total ($ equivalent)	1,015	1,030	855	465	300	250	200

areas of surveillance only are proportionally increased. It is anticipated that the intensive spraying campaign will be largely completed in all areas by 1962.

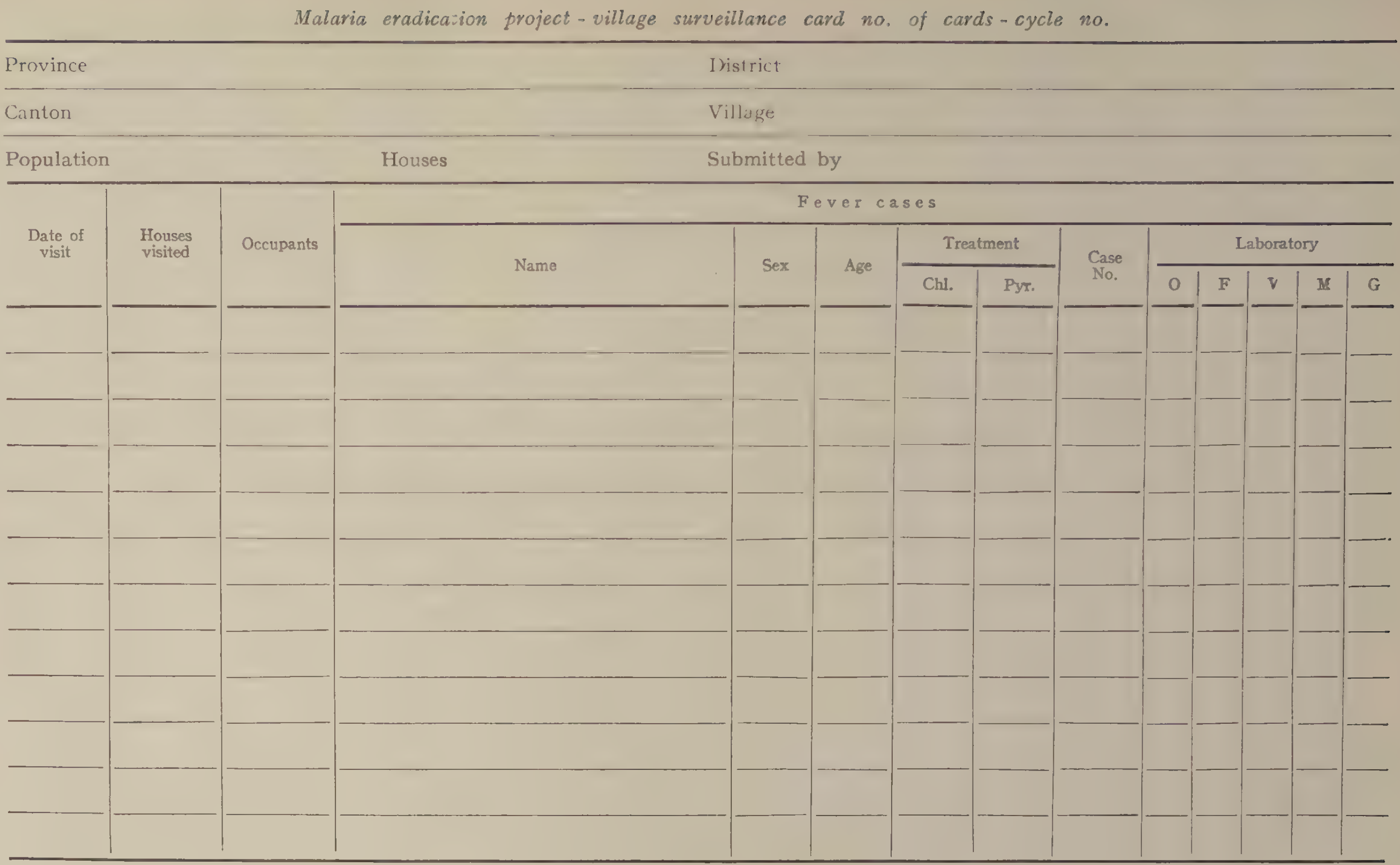
After three years of surveillance in an area, with at least the last two in the absence of a spraying campaign and with no evidence of indigenous malaria, it is planned that surveillance will also be discontinued. The area will then pass into the final maintenance phase of the malaria eradication program when the general health services will have the responsibility for any necessary additional antimalaria safeguards. The first such reduction of the active program is anticipated in 1961.

At this point the Thailand malaria eradication program proposes to introduce a feature of activities designed for ultimate exploration of the entire country to make sure that no hidden malaria foci or hazards are overlooked. The organizational strength released by progressive completion of the active program in major malarious areas (where malaria is a recognized problem) will be transferred year by year to a reconnaissance of minor problem areas. The reconnaissance will be conducted on the same plan as surveillance, but it is believed that one year of active search in each minor area will be all that will be required on the average.

The active programs in both major and minor areas should be completed through 1965, with the antimalaria activities having reached the homes of 22,500,000 people several times each with whatever measures may be required. This projection leaves out an area of about 1,500,000 population (largely represented by municipal Bangkok), but reconnaissance may also be extended to this area in 1966 if deemed necessary. (A natural increment in the population amounting to about 2 % annually is also largely omitted from the projection, since its addition would overly complicate the presentation, and the rapid completion of the program is expected to take care of any increase of this nature.)

Financial plan. The future malaria eradication program in Thailand involves a continuation of three budgets, as in past years — the regular Thai Government Budget, the Counterpart Budget (jointly administered by the government, through the Thai Technical and Economic Committee, and USOM), and the USOM dollar assistance. These three budgets are projected in general terms in Table IV, in accordance with the long-term plans for funding developed by Thailand and the United States.

It will be noted that provision is made for the special program of the laboratory and training centers at Chiengmai and Phrabuddhabat.



Malaria eradication project - village surveillance card no. of cards - cycle no.

Province District

Canton Village

Population Houses Submitted by

			Fever cases										
Date of visit	Houses visited	Occupants	Name	Sex	Age	Treatment		Case No.	Laboratory				
						Chl.	Pyr.		O	F	V	M	G

Fig. 1 (*a*) — Front of village surveillance card.

Date of visit	Houses visited	Occupants	Fever cases										
			Name	Sex	Age	Treatment		Case No.	Laboratory				
						Chl.	Pyr.		O	F	V	M	G

Fig. 1 (*b*) — Back of village surveillance card.

These centers are already functioning in the malaria eradication program and will increase their services, including international training, year by year. This will be true not only for antimalaria activities, but also in other vector-borne disease investigation and control, utilizing the organization, equipment and experience of the Malaria Eradication Project. Toward the termination of the malaria eradication program, provision is made for appropriate development of the two centers and associated field services in national campaigns against filariasis, encephalitis and other vector-borne diseases.

The costs of the malaria eradication program from its inception through 1965 are estimated at about $ 12,000,000 in the dollar and baht budgets. This means a total expenditure of less than $ 0.50 per capita for eradication of malaria from a national population which will considerably exceed 24,000,000 at the close of the program. The average annual costs of a few cents per capita seem low indeed when contrasted with the yearly losses due to malaria prior to control. Such losses have been shown to range in the hundred millions of baht, with serious effects on the national economy and defense (Ayurakitkosol and Griffith, 1957).

The Thai Government has recently reaffirmed its acceptance of the principle of a national effort toward malaria eradication and its recognition of this effort as a national emergency program. Malaria eradication in Thailand has also gained impetus and assistance from the special support given this historic goal by the United States and the United Nations. It is believed that the key to a successful conclusion of the long struggle in Thailand against malaria has been found in the new plans for surveillance. Malaria eradication depends on the totality of two essential house by house campaigns in every significantly malarious area: residual house-spraying to stop malaria transmission, and search and treatment to eliminate the malaria reservoir.

SUMMARY

Plans for malaria eradication in Thailand were formulated in 1955, growing out of an effective nation-wide control program, developed with the assistance of WHO/UNICEF, 1949-51, and USOM, 1951 to the present. The original concept of malaria eradication depended largely on residual house-spraying, evaluated by annual malariometric surveys, with incidental treatment of malaria cases encountered by the field teams. During the past three years it has been

found necessary to provide for increased emphasis on searching out and treating malaria cases.

Over half of the present national population of about 23,000,000 is considered to live in areas where malaria is or has been a major problem. Annual mortality rates per 100,000 population which exceeded 250 prior to control operations have declined to about 47.5 in 1957. Malaria is most prevalent in hilly localities in association with *Anopheles minimus* which is by far the principal vector in Thailand. *A. leucosphyrus balabacensis* and *A. sundaicus* are possibly involved in malaria transmission in a few areas. *Plasmodium falciparum* and *P. vivax* are common in all regions of the country, while *P. malariae* is rarely found.

Most of the Thai people live in farming communities in villages averaging about 500 population (100 houses). Internal population movements complicate the malaria problem in connection with new permanent settlements, seasonal agricultural practices and occasional pilgrimages, labor migrations and tourism. An Antimalaria Coordination Board was formed in 1956 by Burma, Cambodia, Laos, Malaya, Thailand and Vietnam for exchange of information and promotion of inter-country cooperation toward malaria eradication in Southeast Asia.

The Thailand antimalaria program is conducted by the Division of Malaria and Filariasis Control, Department of Health, Ministry of Public Health, with assistance by USOM in technical training, advisory services and financial support. Antimalaria operations in areas of over 12,000,000 population in 61 (of 71) provinces are organized under a central office, eight major headquarters and 30 field stations, reaching most of the major malarious localities.

A new organizational unit plan provides for the technical staffing of each area of about 1,000,000 population with a headquarters unit (one officer and one senior assistant), four laboratory units (one technical assistant and one technical aide each) and 20 field units (one technical assistant and four technical aides each). Training courses and developmental field activities are under way to put this plan into effect this year. The basic field unit performs any of the required antimalaria activities — spraying, survey, surveillance or resumption of spraying (after institution of surveillance) — in its assigned area of about 100 villages (50,000 population).

House-spraying is conducted during the first half of each year, using either D. D. T. or dieldrin 75 % water — dispersible powder, applied with handoperated air compression sprayers to interior house-walls at rates of 2.0 gm./m.^{2} 100 % D. D. T. or 0.50 gm./m.^{2} 100 % dieldrin. Technical surveys are conducted in the last half of the year in 20 % of the villages representative of the most malarious situations. Criteria for interrupting house-spraying include absence of a proven vector from the routine collections, no malaria infected infants (aged 1-11 months), a malaria parasite rate of less than 1 % and a spleen rate of less than 10 % in children (aged 2-9 years), and no significant hazard of malaria resurgence or introduction.

The 1958 antimalaria program includes 7,680,765 population in the house-spraying campaign and 4,551,871 population in areas where spraying has been discontinued on the basis of the above criteria. From one to four years of general house-spraying are considered sufficient; in areas which do not meet the criteria by the third year, surveillance is instituted in lieu of survey in the last half of the next year after the fourth spraying. Further spraying is then limited to malaria foci revealed by the surveillance.

The new plan for surveillance is based on house to house visits by the field units in a bimonthly cycle of the entire assigned area. The surveillance teams concentrate on searching out fever cases, treating them with combined single doses of chloroquine and pyrimethamine, collecting blood films for confirmation of malaria, and public information on antimalaria measures. The laboratory units examine the blood slides and participate in epidemiological investigations which may be conducted by the headquarters units. Three years of surveillance are considered sufficient in the absence of evidence of indigenous malaria and active malaria transmission. Surveillance is fully performed by the antimalaria organization; however, cooperative assistance is proposed from hospitals, health centers and other agencies, and a special surveillance program in agricultural settlements is on field trial.

The malaria eradication program has been projected with USOM assistance to an expected conclusion in 1965, including progressive reconnaissance of all relatively minor malarious areas, as surveillance units are released for this activity by completion of the active program in the major malarious areas. The program will thus eventually reach every home in Thailand, with the possible exception of such large municipalities as Bangkok, with several direct contacts and such antimalaria activities as may be required.

The Thai Government has recently reaffirmed its objective of malaria eradication and has recognized the antimalaria operations as a national emergency program. These actions have been taken in keeping with the resolutions and program of the United Nations and the United States toward world malaria eradication.

ACKNOWLEDGEMENTS

The authors are indebted to the officers and advisers of the Thailand Malaria Eradication Project for much of the basic data necessary to the writing of this paper, especially to Dr. Vimol Notananda and Dr. Term Vajrasthira for material on the experimental surveillance conducted in Northern Thailand, and to Dr. J. Miles Butler, Jr., for assistance in compilation. Gratitude is also due to Dr. D. K. Viswanathan, WHO Regional Malaria Adviser, for his stimulating participation in the discussions of surveillance which have contributed to the plans herein described.

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MALARIA ERADICATION IN TAIWAN, REPUBLIC OF CHINA

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Before the start of the present antimalaria campaign, malaria was one of the principal causes of sickness and death in Taiwan despite the fact that enormous effort and immense sums had been spent to bring the disease under control during the fifty years of Japanese occupation. In 1951, the annual incidence of malaria was estimated to be well over 1,200,000 cases, among the population of 7.8 million, with more than 11,000 malaria deaths per year. The effects of this disease, as a major obstruction to socio-economic progress, on the local populace must have been tremendous.

The current antimalaria scheme was launched in 1952 with valuable assistance from WHO and ICA and the first island-wide DDT residual spraying program was carried out in 1953. The scheme is now converted into an eradication program. A 5-year malaria surveillance project, 1958--1962, is being implemented and it is hoped that the final objective of eradication will be attained before the target year 1962.

Pre-DDT era: malaria problem and epidemiology:

Malaria is most certainly a very old disease in Taiwan. However, official records of the incidence of malaria became available only after the Japanese occupation of the island in 1895. Before 1911 malaria topped the list for morbidity and mortality with over 10,000 malaria deaths per annum when the population of the island was around 3 million (1). A malaria control scheme was launched by the Japanese in 1911 when the first antimalaria station was established in northern Taiwan for detection of parasite carriers by routine blood examination and their treatment using quinine and later atebrine. This scheme has been pro-

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 531-550, 1959

gressively expanded to cover all the highly malarious areas and at the most active year, 1941, there were 214 such stations existing on the island. During the same year there were 3,309 (5.8 per 10,000 population) malaria deaths which was probably the lowest malaria mortality rate in Taiwan up to 1941: Malaria was thus brought under control but transmission had never been interrupted (2).

During World War II, the antimalaria stations having suspended their routine function due to lack of personnel and budget, coupled with the deteriorating social order and diminishing material resources, malaria became a very serious problem and epidemics were rampant in most of the rural areas. Though accurate statistics are not available, it was estimated that annual malaria morbidity was well over 1,500,000 cases toward the end of the war when the island's population was six million.

It was upon this background that the Taiwan Provincial Malaria Research Institute (TAMRI) was established in 1946 through the inspiring leadership and support of the Rockefeller Foundation. Epidemiological studies of malaria were carried out extensively following the establishment of this institution.

Malaria Endemicity — The latest and most comprehensive malaria prevalence survey that was undertaken in Taiwan prior to the implementation of the large scale DDT spraying campaign was the island wide spleen survey in 1953. During this survey more than 140,000 school children of 6-9 years of age were examined for splenomegaly, samples being taken from all over the island including both urban and rural townships. Results (3) of the survey are summarized in Table I, show-

TABLE 1 — *Spleen survey of school children, 6-9 years, in Taiwan, 1953 and 1955*

Spleen rate	Areas	No. of townships surveyed	
		1953	1955 *
76 to 100 %	Hyper-endemic	21 (5.9 %)	1 (0.3 %)
51 to 75 %	Hyper-endemic	40 (11.2 %)	4 (1.1 %)
11 to 50 %	Meso-endemic	237 (66.2 %)	155 (44.0 %)
0 to 10 %	Hypo-endemic	60 (16.8 %)	192 (54.6 %)
Total		358 (100 %)	352 (100 %)
Overall spleen rate		25.5 %	13.7 %

* After 2 years, D. D. T. spraying operations.

ing the endemicity of different townships, together with the results of another similar survey conducted in 1955 after two years of the residual spraying campaign.

The 21 townships where the spleen rate is shown to be above 75 % in 1953 should not actually be considered as holo-endemic areas as the parasite rate among children is rather low (10-30 %) and so they must be considered as hyper-endemic areas (altogether 61 townships, or 17 % of the inhabited land).

On the whole, malaria was found to be hyper-endemic in the western foothill areas and along the coast of eastern Taiwan, whereas large rural areas in the western plain region were meso-endemic and only a narrow strip of lowland along the west coast was rather malaria free. Wu (4) reported that according to surveys in central Taiwan, the most malarious areas were situated between 500 to 1,000 m. of elevation and that very little malaria could be found above 1,000 m.

Another feature of malaria incidence in Taiwan in the pre-DDT days is the possibility of very sharp outbreaks occurring in the areas of low endemicity. Strange enough these are very limited in extent. Invariably such outbreaks have been found to be associated with a considerable increase of *A. minimus,* the main vector species (5).

Generally, *P. falciparum* was the most predominant species before the spraying operations, causing about 50 % of the total infections. The prevalence of *P. vivax,* under endemic conditions, was also high, consisting of some 40 % or more of all parasite carriers, while *P. malariae* infection formed the smallest proportion. In the cases of epidemic malaria, as in the outbreaks seen in the areas of low endemicity, *P. falciparum* was even more predominant over the other two species.

Vector Species and Transmission of Malaria — In all, sixteen species of Anopheles have been identified in Taiwan (6), of which seven species were reported to be naturally infected with malaria parasites according to the early studies(7). However, more recent and extensive studies made by TAMRI (5) have confirmed *A. minimus* as the principal, if not sole vector, and this species was frequently found infected. Moreover some doubt exsists as to the validity of the previous reports pertaining to natural infection in *A. hyrcanus sinensis* as crithidia-like flagellates which have been described in the salivary glands of *A. sinensis* can be easily misinterpreted as sporozoites.

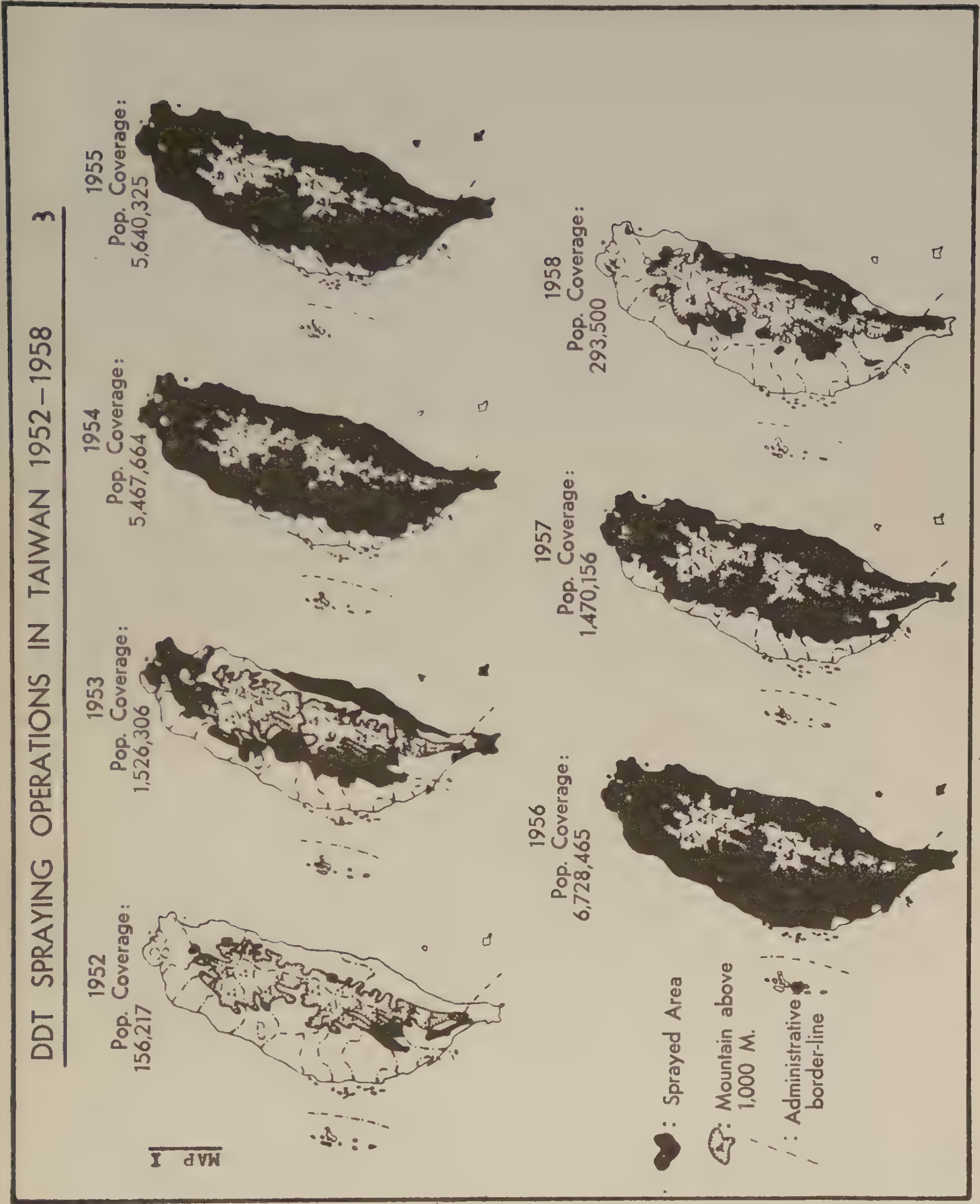
A. minimus was actually found infected from February up to November and it can be consequently assumed that malaria transmission is possible throughout the year. From a 2-year study on the seasonal prevalence of malaria in southern Taiwan, Watson (8) concluded that new infections occurred in every month of the year and that there were two peaks of transmission, April to June and November to January with the greatest incidence of cases falling in May and December.

DDT residual spraying program, 1953-1957:

Residual insecticide spraying of houses for malaria control was first carried out in Taiwan during the period 1946 to 1949 when TAMRI undertook such study projects on an experimental basis. Results of the studies have proved that DDT, when applied by imagocidal spraying at a doses of 2 gm per m^2 of surface, was very effective in interrupting malaria transmission under the local epidemiological conditions.

In late 1951 the Taiwan Provincial Government decided to undertake island-wide malaria control operations based on this new approach. Generous offers of technical and financial assistance from WHO and ICA prompted this decision. A demonstration project was organized in 1952 and a hyperendemic district (Chi-shan district) in southern Taiwan was selected as a demonstration (sprayed) and a check (unsprayed) area for malariometric and entomological observations in conjunction with the residual spraying program. Extensive malaria reconnaissance was carried out throughout Taiwan in 1952 in order to define the hyperendemic areas to be included in the 1952 spraying program, and also entomological and socio-economic studies were conducted in several representative areas with a view to collecting useful data for the planning of control operations in the following years and to gathering baseline data from which to measure the progress.

Island-wide residual spraying operations were conducted during the years 1953-1957 according to the following lines: in general, hyperendemic areas of the island were sprayed for the 5 consecutive years, meso-endemic areas for the 3 consecutive years while the hypo-endemic areas were sprayed once in 1956 (Map 1).


DDT SPRAYING OPERATIONS IN TAIWAN 1952–1958
3
MAP I
1952
Pop. Coverage:
156,217
1953
Pop. Coverage:
1,526,306
1954
Pop. Coverage:
5,467,664
1955
Pop. Coverage:
5,640,325
1956
Pop. Coverage:
6,728,465
1957
Pop. Coverage:
1,470,156
1958
Pop. Coverage:
293,500
: Sprayed Area
: Mountain above 1,000 M.
: Administrative border-line

Year	Population protected	Insecticide used	Area covered
1953	1,526,306	DDT	All areas where the spleen rate was above 35 %
1954	5,467,664	DDT	All malarious areas where the spleen rate was above 10 % including the greater part of the island outside the coastal plains
1955	5,640,325	DDT	Same area as the previous year extended to include mountainous areas
1956	6,728,465	DDT, BHC	1955 area plus hypo-endemic coastal plains (whole island except the cities)
1957	1,470,156	DDT, BHC	Same area as in 1953 to cover all foothill areas

Except on the small island of Lan-yu (Orchid Island) where DDT was sprayed twice a year because of its peculiar housing conditions and holoendemic malaria, the annual cycle was as a rule applied in Taiwan proper. DDT was applied at the dose of 200 mg per square foot but later a mixture preparation of DDT and BHC was used in order to enhance knock-down effect of the insecticide against common pests in an effort to sustain public interest in the campaign. When this mixture was used a square foot of surface received 200 mg of DDT plus 17 mg γ-BHC. Spray was applied to all inside surfaces of a house, including walls and ceilings, as well as to the sides of furniture and underneath beds. Latrines and animal shelters were also sprayed.

As a rule spraying crews were recruited from the respective township and, usually, a malaria technician or sanitarian from the local township health station served as squad leader. The general policy adopted in Taiwan has been to shift progressively the responsibility of field operations to local health authorities in each hsien equal to prefecture or county or township. However, training or personnel, supervision, and the planning or the evaluation of the program always remained in the hands of TAMRI.

It is the consensus of the opinions of many malariologists that residual spraying must be interrupted as soon as new transmission has been stopped and the remaining malaria cases can be detected and treated by a suitable surveillance organization (9). The spraying operations were withdrawn from the hypo and meso-endemic areas in 1957, where the pre-control spleen rate was below 35 %, and beginning from 1958, DDT spraying has been stopped in a large part of the formerly hyper-endemic areas except in some areas where residual foci of malaria can be found.

On the other hand malaria surveillance has been introduced since December 1954. The basic policy then was to make concurrent use of local township technicians in the surveillance work on a part-time basis. This policy had its obvious advantages in making use of the trained technicians who are familiar with their villages and people, and a saving a considerable expense which would otherwise have been incurred by the employment of additional staff. However, at the same time, it proved to be the most serious drawback as the public health duties of these technicians frequently interfered with the schedule of surveillance work.

Generally, there were two types of surveillance units, stationary and mobile, operating during this period (Dec. 1954 to June 1958). The «stationary» units were located in hyper and meso-endemic townships, each consisting of one local technician who would conduct house-to-house surveys of fever cases and post-operational children (children born after the initial spraying operation) in the most malarious villages within his township. The «mobile» units were organized with TAMRI and local technicians, each unit consisting of 5 persons working full-time for this program. There were 10 mobile surveillance units operating during 1956-1957; they were distributed to various parts of the island moving from one township to another and making coverage of the areas left out or improperly covered by the «stationary» units. During the period from December 1954 through June 1958 these malaria vigilance units, both stationary and mobile, have collected 496,595 blood smears from infants, post-operational children, and fever cases among other age groups, resulting in the detection of 784 parasite carriers (positive rate 0.16 %) to whom full-course antimalaria treatment was given. Evolution of surveillance planning and analysis of results were reported elsewhere by Ch'en *et al.* (10, 11).

Results of residual spraying campaigns and present problems of malaria:

After the island-wide DDT residual house spraying campaign during the five years from 1953 to 1957, a progressive but remarkable decline has occurred in the *plasmodium* infection rate throughout the formerly malarious areas as indicated by the results of annual parasite surveys (Table II). Since 1951 an extensive parasite survey has been undertaken each year at 150 representative localities, selected from the formerly hyper-endemic areas, and the survey was conducted simultaneously on the 17th of December each by 150 local malaria technicians, taking blood slides from 100 pre-school children of 2-5 years of age randomly sampled from each locality. Microscopy of these blood slides was done at the TAMRI laboratory.

On the whole it can be assumed that after two years of spraying, malaria transmission was practically interrupted in most parts of the malarious areas. This was evident from the results of the infant parasite surveys: From December 1954 up to May 1956, 63,460 blood smears were collected from infants under 12 months of age and only eight positive cases were found in three residual foci. In the Chi-shan district, the original demonstration area sprayed in September 1952, the infant parasite rate which was 14.72 % before the spraying operations was brought down to zero as early as November 1953 and has remained negative since that time.

Adults of *A. minimus* completely disappeared from the sprayed houses immediately after spraying and remained absent for a long time. Recent searches for this mosquito revealed that adult specimens could not be found in the sprayed houses even in the areas where the spraying has been discontinued since 1956, although breeding of this species has been occasionally found (12).

Through malaria surveillance activities and other investigations, a limited number of parasite carriers has been detected: The number of laboratory confirmed malaria cases for all Taiwan was 488 in 1956, 434 in 1947, and only 157 during the first 6 months of 1958. Age distribution and the species of infection of these cases are summarized in Table III.

These parasite carriers were detected through extensive infant surveys, mass blood surveys in suspected malaria foci, fever-case surveys in schools and by home visitation, and through other surveillance measures. It appears that the positive rate is low considering the large number of blood slides examined in each period since 1956 onward. However, transmission has been demonstrated, though it is confined to some limited foci, throughout the whole period under study as indicated by

TABLE 2 — *Result of island-wide simultaneous malaria parasite surveys among pre-school children, 1951-1957*

Date of survey	No. of townships included	No. of children examined	Positive cases					Para. rate	DDT sprayed
			P. v.	P. f.	P. m.	Mix.	Tot.		
Dec. 17, 1951	139	13,885	375	669	84	70	1,198	8.63 %	
Dec. 17, 1952	143	14,213	532	778	34	41	1,385	9.74 %	
Dec. 17, 1953	145	14,419	245	337	46	32	660	4.58 %	Mar. 9-Nov. 13, '53
Dec. 17, 1954	147	14,614	90	68	10	5	173	1.18 %	Feb. 15-Oct. 31, '54
Dec. 17, 1955	148	14,759	12	9	5	4	30	0.20 %	Mar. 7-Sep. 27, '55
Dec. 17, 1956	150	14,825	0	2	0	0	2	0.01 %	Mar. 19-Dec. 3, '56
Dec. 17, 1957	150	15,391	0	0	1	0	1	0.006 %	Feb. 26-Oct. 21, '57

TABLE 3 — *Age distribution and plasmodium species of laboratory confirmed malaria cases detected in Taiwan, January 1956 to June 1958*

Period	No. of cases	Dist. by age groups					Dist. by plasmodium Sp.				Total exam.
		0-1	2-4	5-9	10-14	15 & over	P. f.	P. v.	P. m.	Mix.	
Jan.-June, '56	307	6	40	82	76	103	86	176	34	11	64,576
July-Dec. '56	181	3	27	42	17	92	63	80	35	3	106,240
Jan.-June, '57	155	7	28	46	20	54	45	71	36	3	164,489
July-Dec. '57	279	6	35	58	38	142	102	109	64	4	133,195
Jan.-June, '58	157	4	23	39	30	61	36	92	27	3	149,478
Total	1,079	26	153	267	181	452	331	528	196	24	617,978

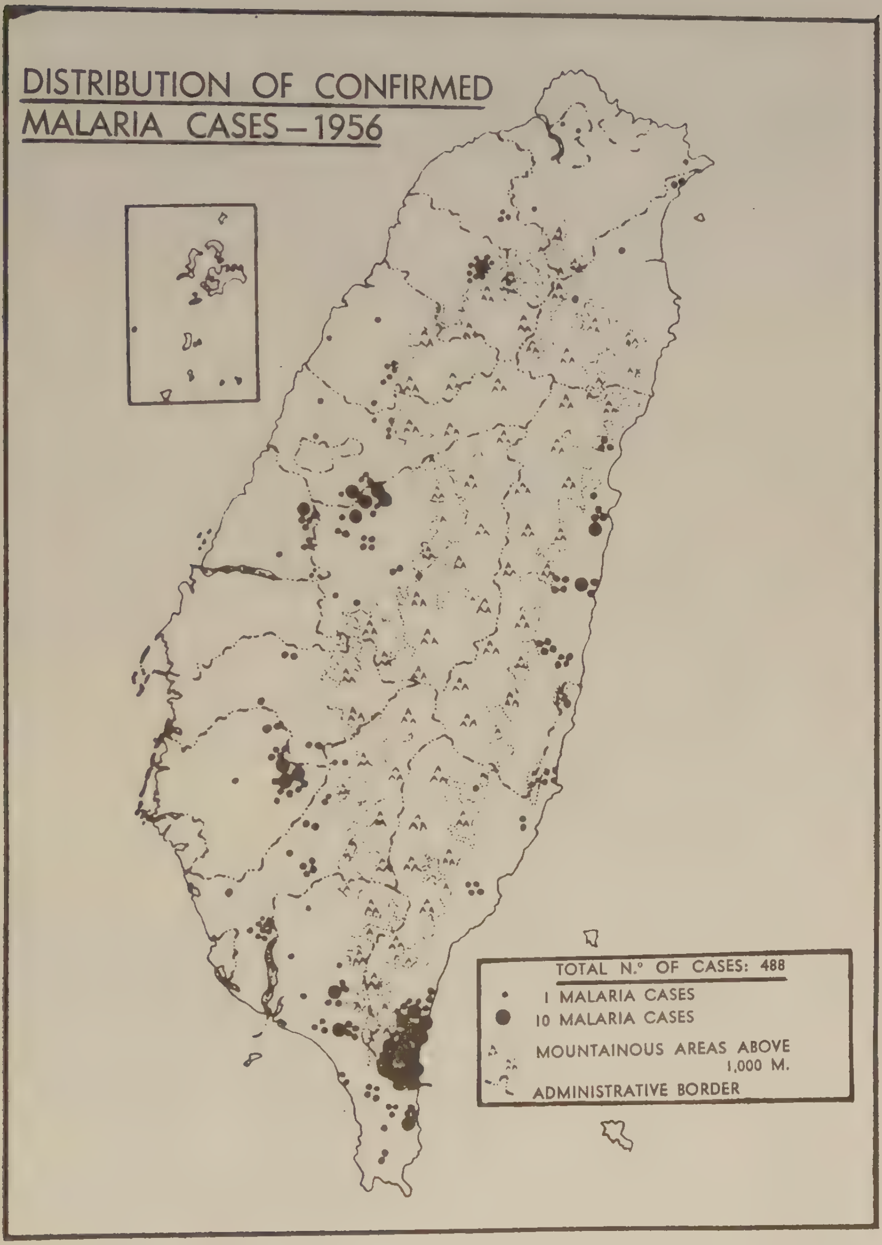
* Because of the Asiatic influenza epidemic a great number of fever cases was included in the blood examination during this period.

the results of infant surveys and the considerable number of positive cases which have been found among the age-group of 2-4 years which consists of post-operational children, or children born after the initial DDT operation in the respective areas. Taking into consideration the fact that not only *P. falciparum* infection but also *P. vivax* and *P. malariae* infections were found among infants and post-operational children, it must be assumed that recent malaria transmission encountered in some foci areas involved all three species of *plasmodium* though in varying proportions. Among the older age-groups, such as school children and adults, patients with benign, tertian and quartan malaria were detected in much greater number than the cases with malignant tertian infection. However, it would be safer to call every patient with malaria, regardless of the species of infection, a «new» case, unless the contrary can be proved by follow-up case investigation.

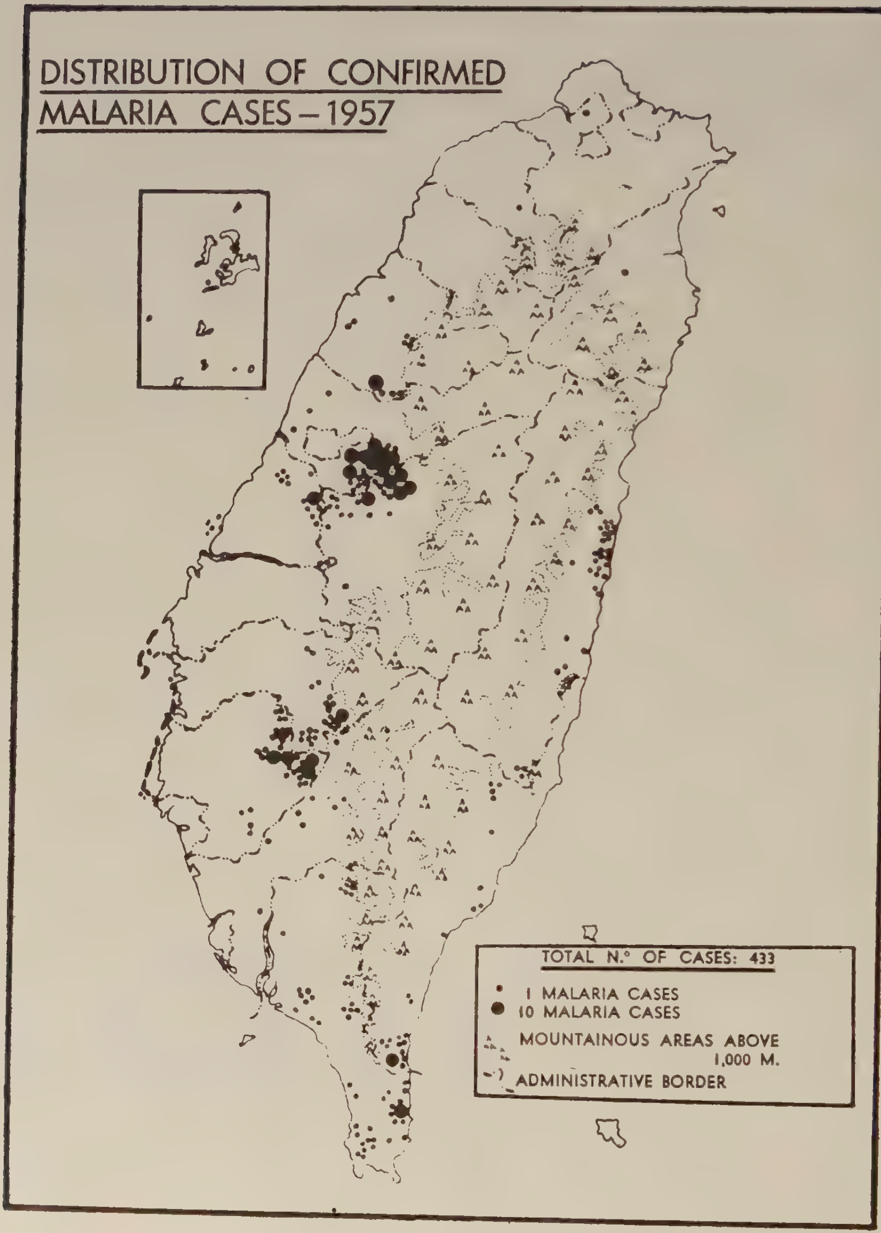
Geographical distribution of the malaria cases found in 1956 and 1957 is shown in maps 2 & 3, respectively. It is gratifying to note, from the standpoint of malaria eradication in Taiwan, that malaria has been practically eliminated from the north, north-east, and from vast rural areas in the plains of the west and south-west. The great majority of the cases were concentrated, forming residual foci, in mountains and foothills of the central (Tai-chung and Nan-tou hsiens), and south-west (Tai-nan hsien) areas, and along the south-east coast (Hua-lien and Tai-tung hsiens). It is interesting to note that residual foci detected in the central and south-west are situated along the upper streams of the rivers Tso-shui and Tzeng-wen.

General characteristics inherent in the active malaria foci discovered in Taiwan have been reported by Hsieh and Liang (13). Generally there are two types of active malaria foci; those found in unsprayed places and those still remaining in areas which have been sprayed continually for several years. Typical foci of the first type are discovered in wood-cutters' settlements and similar situations in which a group of non-immune laborers is engaged, during certain periods of the year, in some productive enterprises and other construction projects that are located in the potentially malarious mountainous regions. The shelters housing these laborers being of a temporary nature, are frequently not known to our spraying squads. Malaria transimission in these foci usually culminates in a localized outbreak, with *P. falciparum* infection being most predominant, and is always associated with *A. minimus*. It is

MAP II


DISTRIBUTION OF CONFIRMED MALARIA CASES – 1956
TOTAL N.° OF CASES: 488
1 MALARIA CASES
10 MALARIA CASES
MOUNTAINOUS AREAS ABOVE 1,000 M.
ADMINISTRATIVE BORDER

Map III


DISTRIBUTION OF CONFIRMED MALARIA CASES – 1957
TOTAL N.° OF CASES: 433
• 1 MALARIA CASES
● 10 MALARIA CASES
MOUNTAINOUS AREAS ABOVE 1,000 M.
ADMINISTRATIVE BORDER

obvious that in such cases emergency DDT spraying is the first step to be taken to stop malaria transmission and that drug treatment should be given to the whole affected population.

On the other hand, residual foci in the sprayed areas have, as a rule, some interesting epidemiological features. The number of malaria cases detected in these foci is usually small but they are dispersed over a large area of formerly hyper-endemic foothills and valleys. Contrary to the active foci in unsprayed areas, *P. vivax* and *P. malariae* are the predominant species of infection in residual foci in the sprayed areas. Even in the absence of treatment of the known positive cases and residual house spraying, as in the case of the Nan-hsi focus which was purposely omitted for epidemiological studies, these foci have no tendency to expand. The possibility of a low rate sporadic transmission is, however, evident in view of the fact that positive blood slides have been demonstrated among infants and children born after the DDT spray. *A. minimus* is usually present in these foci but other anopheline species, such as *A. maculatus,* have been suspected from the circumstancial evidence to play a secondary role in transmission. Factors contributing to the continued existence of these foci have been studied and the following reasons are thought to be the more important ones: remoteness of the foci and improper spray coverage, sparsely distributed houses with special housing conditions, loosely built cane or bamboo houses or the coating of the inner walls or partitions with soot from the built-in cooking fire. The results of biological tests conducted in some residual foci have demonstrated that the lethal action of DDT is greatly hampered by soot deposits. All the above-mentioned factors indicate that house spraying in residual foci in the sprayed areas must be repeated with a shorter interval than the usual once-a-year practice in order to stop transmission. A semi-annual spray round, already adopted in Lan-yu island where housing conditions are poor, proved to be very successful.

Another interesting feature which deserves mention in regard to the recent pattern of malaria in Taiwan is the relatively small number of residual cases of malaria, relapses or long-standing infections, throughout the vast formerly malarious areas in which transmission had been completely stopped. Occasionally small numbers of cases were reported by the surveillance technicians from the now «healthy» areas: Further investigation of these cases has demonstrated that the majority of them were «imported», having contracted infection in active foci.

Implementation of a 5-year malaria surveillance program (1958-1962):

Thanks to the generous assistance of WHO and ICA, a 5-year malaria surveillance program is being implemented in Taiwan with the definite objective of achieving malaria eradication before 1962. To attain this goal a major problem must be solved, that is the detection, followed by prompt and effective elimination, of active foci as well as all remaining malaria cases, the basic process of a surveillance program.

Area definition — For the practical purpose of implementing an efficient surveillance, the whole island has been divided into 5 regions with different epidemiological connotations. These are: *Region 1* which contains active malaria foci, either showing evidence of active transmission or with a large number of parasite carriers showing an overall parasite rate of over 2 % or a *P. falciparum* infection rate of over 1 %; (The population of this region is about 6000); *Region 2* which contains potential malaria foci including the areas of Region 1 after an emergency control, areas with occasional indigenous cases or others with residual or imported malaria cases and the presence of *A. minimus* breeding (Population is about 300,000); *Region 3* being the formerly hyper-endemic areas with a fair number of residual or imported cases but no indigenous cases (population is 1,200,000); *Region 4* being formerly the meso or hypo-endemic areas without indigenous cases of malaria (population is 1,500,000); and the *Region 5* being the non-malarious areas (population is 6,000,000). As the project progresses, each area will be redefined until Region 5 covers the whole island.

Surveillance organization — The overall planning, implementation and supervision of the surveillance scheme are the responsibility of TAMRI. At the local level there are 22 hsien supervisors, one for each hsien, recruited from the respective hsien health center, who are the counterpart personnel to the TAMRI supervisors to see the program is carried out within their own territories. For a township with more than one surveillance technician a senior member is assigned as the township supervisor.

MAP IV

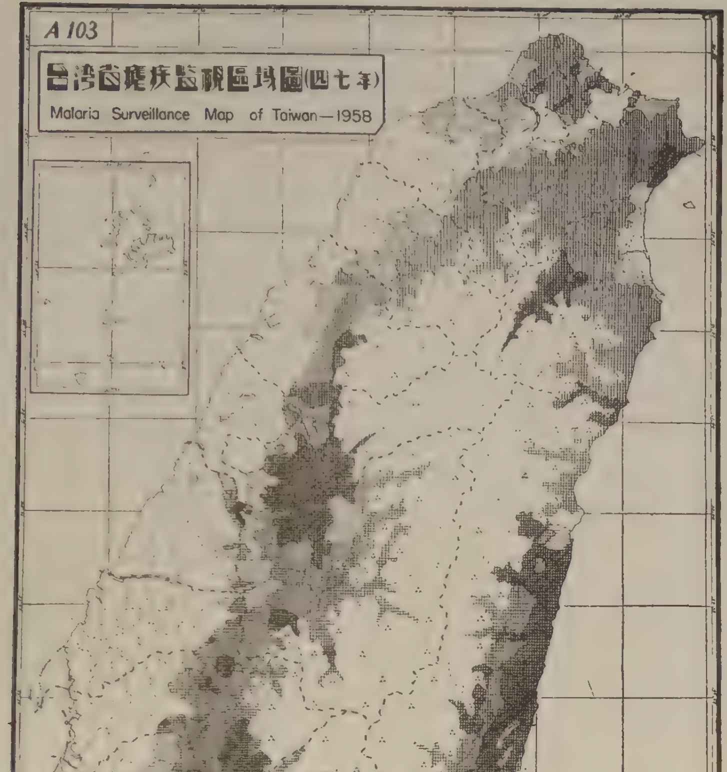

A 103
台灣省瘧疾監視區域圖(四七年)
Malaria Surveillance Map of Taiwan—1958
緊要區 Active Malaria Foci
戒備區 Potential Malaria Foci
搜索區 Formerly Hyperendemic Areas
警戒區 Formerly Meso-or-Hypoendemic Areas
查報區 Non-malarious Areas
一千公尺以上高地 Mountainous Areas above 1,000 m.
縣市界 Administrative Border-line

TABLE 4 — *Malaria surveillance measures in Taiwan*

Measures	Area				
	I	II	III	IV	V
1. *Case Detection*					
1.1 Malaria case reporting	+	+	+	+	+
1.2 Visits to medical units	Monthly	Monthly	Monthly	Monthly	Monthly
1.3 Case investigation and follow-up	»	»	»	»	»
1.4 School fever case survey	»	»	»	»	—
1.5 House-to-house fever case survey	»	»	Annually	—	—
1.6 Infant survey	»	Quarterly	—	—	—
1.7 Mass blood survey	Quarterly	—	—	—	—
2. *Anti-parasite Measures*					
2.1 Radical treatment of cases	+	+	+	+	+
2.2 Single dose treatment to suspected cases	+	+	+	+	+
2.3 Single dose treatment to whole population	Monthly	Semi-annually	—	—	—
3. *Anti-mosquito Measures*					
3,1 Residual spray of carriers' house	+	+	+	—	—
3.2 Ann. Res. spray of whole area	+	+	—	—	—
3.3 Residual spray of new structures	+	+	—	—	—
3.4 Emergency residual re-spray of the whole area	+	—	—	—	—
3.5 Other anti-mosquito measures	+	—	—	—	—

In Regions 1 and 2 which contain active and potential malaria foci that bear the most significant implication on the success or failure of the eradication campaign, surveillance measures are carried out by 110 full-time technicians who are employed by TAMRI and placed under its direct control. One technician usually covers an area of 1,000-3,500 people; the number of technicians assigned to each area would depend on the local malaria incidence and on the topographical features of the area.

The malaria surveillance program in Region 3 to 5 is carried out by 403 local township technicians, working part-time for this project for an average of 5-10 days per month.

Blood smears collected during the survey are sent to TAMRI for examination. At present the laboratory at TAMRI can examine about 75,000 smears per month. Besides, there are 28 local malaria technicians posted at various township health stations who take care of most of the blood slides forwarded from practicing doctors and medical institutions for confirmation.

Entomological surveillance is an important part of the general surveillance scheme, which is implemented by the TAMRI Entomology Section personnel assisted by 10 full-time entomological field assistants. 110 full-time technicians assigned to Regions 1 and 2, primarily as blood-film collectors, also make monthly anopheline collections at routine catching stations. The emphasis of this program is placed on routine checking of *A. minimus* to see whether its distribution will extend or not after the withdrawal of spraying, and on the periodical investigation of the development of insecticide resistance which has not been confirmed so far among the Taiwan anopheline species (14).

Residual house spraying operations, either regular or emergency programs, are conducted by the separate spraying squads which are supervised by the TAMRI Engineering Section. Existing local surveillance technicians often serve as the squad leaders, but spraying operators are recruited among temporary local laborers only during the period of operation in each area.

Surveillance measures — The basic process in a surveillance program is an active and passive search for cases of malaria of which active search is the more important. Malaria is now a reportable disease in Taiwan and the Provincial Gazzette order has stipulated that all medical doctors, either in private practice or government service, should report all malaria cases, both confirmed and merely suspected on a clinical basis, to TAMRI or hsien health centers. The report must be corroborated with a blood smear taken from the patient. In order to reach full understanding and co-operation, monthly visits are made by the surveillance technicians to all medical officers in government or private practice throughout the island. Active search is carried out by house-to-house fever case surveys, school fever case surveys, case investigations and follow-up, infant surveys and mass blood surveys. Different measures for searching for cases are applied to each region with varying intensity as prescribed by the need of the respective area from the stand-point of malaria eradication. The method and the intensity applied to each region are summarized in Table 4.

Once a malaria focus is uncovered all available control measures are mobilized to prevent further spread and to eliminate the potentiality of transmission as expeditiously as possible. To all the known parasite carriers, radical treatment with the full-course of antimalarial drugs is given. Single dose treatment is given to all suspected cases of malaria and fever cases at the time when a blood smear is taken for examination. Mass treatment with single doses of chloroquine, pyrimethamine, or a chloroquine-pyrimethamine combination is applied in Regions 1 and 2 at different intervals.

DDT and other chlorinated hydrocarbons are still very potent insecticides against the local species of anopheline mosquitoes. In Regions 1 and 2, where there is still a danger of transmission, residual spraying is applied to all structures once a year. Active foci many receive an additional round of spray if so indicated after epidemiological investigation. New structures in Regions 1 and 2 are sprayed immediately they are discovered and parasite carriers' houses in Region 3 may be sprayed when indicated by epidemiological considerations. Anti-parasite and anti-mosquito measures to be applied in various regions are also shown in Table IV.

SUMMARY

This paper presents a brief account of the problem of malaria in Taiwan in the past, its control with DDT since 1953, and the current campaign aiming at the eradication to be achieved before 1962. Malaria is an old problem in Taiwan and has long topped the list of local endemic disease. Even as late as

1952, 1.2 million cases of sickness were attributed to malaria with more than 10,000 deaths when the island's population was just over 8 million.

The island-wide DDT residual spraying campaign was started in 1953. Since then the hyper-endemic region and adjacent areas with an aggregated population of 1.5 million was sprayed 5 times until 1957, spraying being conducted once a year at the rate of 2 gm DDT per square metre. Other malarious areas of the island were sprayed 3 times during 1954 to 1956, the largest population coverage in a single year being 6.5 million including the hypo-endemic region.

A. minimus, the principal vector species in Taiwan, has proved very susceptible to residual insecticide, and in the meso and hypo-endemic areas this species has been practically eliminated although DDT spray was stopped two years ago. New transmission has been stopped except in some residual foci and, consequently, a striking reduction in malaria prevalence has occurred as shown by the usual malariometric indices. A parasite rate obtained from the island-wide sampling of pre-school children in hyper-endemic villages has dropped from 9.74 % in 1952 to 0.006 % in 1957. Through the implementation of a malaria surveillance scheme only 488 microscopically confirmed cases were detected in 1956 the whole of Taiwan and 434 cases in 1957.

The present epidemiological features of malaria have been discussed. Residual foci of malaria were discovered in the sprayed areas in the formerly highly malarious foothills in central, south-west, and eastern Taiwan. Occasional transmission foci were detected among laborers' camps in the hinterland which have never been sprayed. Residual cases of malaria are rather scantily in the lowland rural villages from which malaria has been practically eradicated.

An intensive 5-year malaria surveillance program, supported with the funds from ICA and WHO, is being implemented using measures carefully evolved to cope with the local epidemiological conditions. It is hoped that malaria eradication will be completed before 1962. Thereafter, the surveillance activities will be incorporated with the general public health service.

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GENERAL DISCUSSION

Dr. J. M. **Andrews** (U. S. A.) — In reference to Dr. Alvarado's allusion to the monetary support of overseas malaria eradication with U. S. A. funds, I have the following information for the interest of this Section.

At the last Congress of the U. S. A., a proposal was made that an investigation should be launched concerning the expenditure of large amounts of appropriated funds for disease control overseas.

Accordingly, it is my understanding that a Congressional group will visit in the near future various countries in which American resources authorized by Congress for health proposes are being expended Malaria eradication projects will certainly be included. Probably some of the countries represented by persons in this town will be visited.

I respectfully and earnestly urge that if such contacts are made, that the responsible health authorities and advisers will make honest, forthright presentations of their programs, accomplishments, problems, and plans with reference to malaria eradication and other public health activities.

Dr. A. **Gabaldon** (Venezuela) — *Comments on Dr. Alvarado's paper* — In congratulating Dr. Alvarado and his co-workers for their very interesting paper I would like to make at least the following remarks: (1) In reference to the historical summary showing the succession of events in malaria eradication in the Americas, I would prefer to see the date 1945 and the name of Venezuela before that of 1947 and that of the United States of Americas, as it has been recognized that the first nation-wide spraying program designed to cover all houses of the malaria area was our program as stated by Dr. Russell, here present, who knew personally our work in 1946. (2) The generalization in reference to «a degradation of the national malaria services» after 1950 had at least one exception: Venezuela, where the eradication area incrised from 131.954 sq. kms. in 1951 to 248.700 sq kms. in 1954. (3) To be sincere I must add that I was expectating in the paper under discussion some reference to the possible influence the contribution published by Dr. Berti and myself in September 1954 had on the resolution on malaria eradication, in the Americas adopted by the Pan American Sanitary Conference in October, particularly when the manuscript was in the hands of Drs. Soper and Alvarado since March of that year. In the paper I refer to is presented the largest area of malaria eradication reported from the tropical zone, which we suspect encouraged the adoption and implementation of that resolution.

Dr. PAUL RUSSELL (U. S. A.) — This morning's speakers are to be congratulated on their most interesting and stimulating reports. Certainly, the results here reported would have seemed fantastically impossible if predicted in the years prior to DDT. They constitute solid evidence that malaria eradication is indeed feasible, East and West. The leadership of the WHO and PASO has been brilliant and continuous and the support of UNICEF, ICA, and of local governments has been indispensable.

No one believes that malaria eradication is easy. But that it is possible becomes increasingly evident. However, there are still serious problems and I am glad that Doctor Pampana has stressed the need for further basic research and that WHO supports this view.

In regard to Doctor Gabaldon's remarks, I agree that the first country to make a definite program for nation-wide malaria eradication, based on the new weapon of residual spraying, was Venezuela, in 1945.

Dr. H. T. SOEPARMO (Indonésia) — Congratulations to the speakers of this session who gain so high success in the malaria eradication in the various countries special for Dr. U. Sandhinand and Dr. C. T. Chen, as direct neighbours I express my special congratulation and I hope I can follow their steps in my country. My attention is drawn very much for the malaria eradication program. As Dr. U. Sandhinand mention that in Thailand he has much troube with migration people, I would tike to ask, are there guarantise measures carried out in the various parts of the country? If there are, I would like to know how it is executed?

Thank you very much.

Rr. U. **Sandhinand** (Thailand) — Migration of people is a real problem in eradication program in Thailand. The field units (a unit of 5 assigned to 50.000 population) have the duty of finding the fever cases from house to house visits, both in permanent and temporary shelters, where these people stay. Over 70 % of this migration can be covered.

Rr. H. **Trapido** (U. S. A.) — When one is concerned with eradication rather than control it would seem that statistics on area as well as population are very much to the point. In eradication the last few cases scattered in remote sparsely populated areas present a formidable problem. Thus we need to consider population in relation to density.

Dr. **Fred L. Soper** (U. S. A.) — Called attention to the great enthusiasm of the nations of the Americas, since the action of the XIV Pan Am. Conference in 1954 in recomending a program for the continental eradication of malaria, in transforming control programs to malaria eradication campaigns. All countries of the Americas, with a single exception, have assumed responsibility for national eradication campaigns, and are actively developing such campaigns.

With regard to the remarks of Dr. Gabaldon, mentioned the fact that malaria eradication in U. S. A. was projected before DDT was available. The Americas were exceptionally fortunate in having two tropical areas, Venezuela and British Guiana, where malaria had been carefully studied for many years, and in the fact that these two areas were among the first to receive, use and study residual insecticides.

There is surely more than enough glory and satisfaction for all who have had any part in the program for the eradication of malaria. It is certain that when this tremendous job is finished, some medical historian will study the reports and give credit for primacy where due; knows that there was no attempt on part of Alvarado to depreciate the value of the contribution of Venezuelan workers in development of American program.

Referred to the 1950 Symposium on National Malaria Eradication programs at Savannah Georgia where reports were presented by Brazil, British Guiana, United States and Venezuela and his (FLS) statement that malaria could be eradicated from the Americas within a five year period whenever the countries decided to take full advantage of the coordinating facilities of the international health organizations.

Administratively it is of course going to take a longer period of time, but those who knew malaria control difficulties of period before World War II, cannot fall to be stimulated and gratified by what is happening not only in the Americas but in all parts of the World, as presented in numerous reports at this Congress.

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 551-554, 1959

2ND SESSION — *Friday, September 12th, 11:00 to 12:30 a.m. Romm D*

The meeting was held under the Chairmanship of Dr. Justin M. Andrews and Dr. George Giglioli.

The Rapporteur was Dr. Fernando Bustamante and the Secretary was Dr. Manuel T. V. de Meira.

The following papers were presented and discussed:

ERADICATION OF MALARIA IN VENEZUELA

Dr. ARNOLDO GABALDON [1]

Of the 21 republics in the Western Hemisphere, Venezuela was proportionately to her territory the one most severely hit by malaria. The areas which were infected cover a surface of 600,000 square kilometers inhabited by 4,500,000 persons. The nation-wide campaign against malaria in this country, begun in 1945, was based on DDT indoor residual spraying, and had as its aim «the eradication of malaria from Venezuela» by «protecting all the houses of the malaria zone, even those of sparsely populated or mildly malarious districts» (Gabaldon, 1949). It was also the first nation-wide campaign organized with such an objective (Russell, 1952). The initial plan contemplated having the whole country malaria-free by 1955, after spraying 100 per cent of the houses of the infected zone. This plan, however, was not feasible due to circumstances explained elsewhere (Gabaldon and Berti, 1955).

THE PROBLEM

There were in Venezuela around one million malaria cases per year. Before the campaign the median malaria death rate was 164 per 100,000, but many of the primary political divisions had death rates above 500 and even 1000. Birth rates were lower in the highly infected areas than in the non malarious ones, and frequently the first had negative vital indexes. During the first third of this century a marked decrease in population was observed in the Llanos, a region with 301,000 sq. kms., one of the most aflicted areas. It is evident that malaria was for Venezuela the most important public health problem and the main obstacle for her economic and social development.

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[1] From the División de Malariología, Dirección de Salud Pública, Ministerio de Sanidad y Asistencia Social, Maracay, Aragua, Venezuela.

Of the 30 anopheline species found in Venezuela six are connected with malaria transmission: *A. albimanus, A. albitarsis, A. aquasalis, A. darlingi, A. nuñez-tovari* and *A. pseudopunctipennis*. Although the main vectors are *A. albimanus* and *A. darlingi,* the last one being the more potent, malaria in presence of each one of the others has been found, and in some areas, where *A. nuñez-tovari* and *A. aquasalis* are the vectors, intensity of transmission was as high as in areas where the main vectors were present. The anthropophilic specimens of *A. albimanus, A. albitarsis, A. darlingi* and *A. pseudopunctipennis* are mostly indoor biters and resters, but those of *A. aquasalis* and *A. nuñez-tovari* are also outdoor biters and resters.

The facts mentioned above are important in order to understand the present status of malaria in Venezuela. In areas where the vectors were practically only indoor biters and resters, the disease was *responsive* to the insecticide and eradication was obtained. In other areas, with outdoor biters and resters as *A. aquasalis* and *A. nuñez-tovari,* malaria has been *partially refractory* and is still prevalent although considerably reduced.

Malaria parasites were unevenly distributed. In areas of high endemicity *Plasmodium falciparum* was the more common, around 60 per cent of the infections being due to that parasite. *P. vivax* was the predominant species, always above 50 per cent, in areas of low endemicity and epidemicity. *P. malariae* was the least frequent of all, generally less than 10 per cent of the infections were due to it. Mixed infections were more prevalent in areas of high endemicity, usually not less than 15 per cent of all cases, and were less abundant in areas of low endemicity and epidemicity.

All epidemiological forms of malaria were present in Venezuela: (*a*) areas of high endemicity and low epidemicity, (*b*) areas of high epidemicity and low endemicity, (*c*) areas of low endemicity and low epidemicity, and (*d*) areas with intermediate degrees of endemicity and epidemicity. Marginal zones of the malarious areas were wider some years and narrower other years, according to the paraquinquenal periodicity of the disease, typical of the country.

Holoendemic malaria did not exist in Venezuela, as the important anophelines responsible for transmission had a lower vectorial capacity than African and Oriental species (Gabaldon, 1948). But, on the other hand, epidemicity reached high levels. During epidemic years, in some municipios, the general death rates were frequently above 70 per 1000 inhabitants and the infant death rates above 500 per 1000 births. In municipios of high endemicity general death rates were usually between 30 and 40 and the infant death rates above 250. As in these figures the only possible mistakes could have been only the result of under-registration, it is easy to understand the dreadful impact malaria represented for Venezuelans.

THE PROGRAM

The nation-wide campaign against malaria in Venezuela has been carried from 18 field stations, centers of the operational zones. In each zone there are three services: epidemiology, insecticides and administration. In these zones there are 34,049 localities where work has been performed. Through the medical services available, private or governmental, and through house to house visits by rural visitors, the field services of epidemiology have knowledge of all microscopically confirmed cases of malaria occurring in the zone, and therefore in the whole country. Slides are taken to all fever cases going to medical dispensaries or hospitals or found in those visits. To complete their monthly quotas, rural visitors take also slides from sickly-looking persons and from children, and sometimes of the whole population. An inquiry is made of all positive cases in order to classify them following the suggested international classification.

DDT house spraying of the whole malaria zone of Venezuela was no small or easy task. It involved treatment of all houses in or near the neighbourhood of areas where either parasites or known vectors had been recorded. Many difficulties were found owing to the large size of the area, the low density and scattered distribution of the population, the lack of good roads in many places, the fault or defficiency of maps, etc. The spraying program was from the first on as large scale as possible. But the program was an expansive one, incorporating new areas every year, and therefore different from the total coverage from the first year advised at the present. By the fifth year 84 per cent of the houses to be sprayed had been treated, and due to absence of the disease in the marginal areas the original aim of spraying 100 per cent of the houses was not required.

THE RESULTS

In 1954 it was reported from Venezuela a contiguous area of 180,000 sq. kms. from which malaria had been eradicated, the area being the first and largest one known at that time from the tropical zone (Gabaldon and Berti, 1954). This report appeared before any resolution on malaria eradication were adopted by the international health organizations.

Of the 600,000 sq. kms. originally infected with malaria there was at the end of 1957 an area of 372,600 sq. kms. where the disease has been eradicated, that is, where no indigenous cases have been found from three to nine years. In this area live 3,065,000 people and is the largest reported zone of eradicated malaria in the world, outside the United States of America. An other area, of 36,465 sq. kms., with 479,400 inhabitants, had no indigenous cases in the last one or two years. There is only one area, of 190,394 sq. kms. and 972,708 inhabitants, where some cases are still found (Table 1). The importance of these figures can be evaluated when compared with those of other countries of the Western Hemisphere, excluding the United States of America, which are in the temperate zone. In 1956 there were in these countries 432,912 sq. kms., with 6,765,000 inhabitants, where malaria had been eradicated according to figures published by the Pan American Sanitary Bureau (1957). Of these, Venezuela had 361,049 sq. kms., or 83 per cent of the territory of the eradicated area, and 2,879,000 inhabitants or 43 per cent of population living in that area.

The persistence of malaria in the 76 municipios of the area still infected requires some discussion. First of all a marked change in the relative frequency of the parasites has taken place. *P. falciparum*, formerly responsible for more than 50 per cent of the infections, is at present practically eradicated. In the last three years, of the 2 327 indi-

TABLE 1 — *Venezuela: Summary data of the eradication program*

Groups of municipios according to first year without indigenous cases	A (1949)	B (1950)	C (1951)	D (1952)	E (1953)	F (1954)	G (1955)	H (1956)	I (1957)	J still infected
Population, July 1st. 1958	1.569.674	405.040	231.295	219.220	178.555	323.260	137.886	266.111	213.591	972.708
Area in sq. km.	131.954	24.984	42.802	48.961	56.713	55.631	11.556	28.273	8.192	190.934
Inhabitants per sq. km.	11.9	16.2	5.4	4.5	3.2	5.8	11.9	9.4	26.1	5.1
Percentage of rural population	50.0	40.2	68.1	61.7	62.2	65.7	44.7	40.3	46.8	42.1
Inhabitants per physician	3.000	2.154	3.126	4.567	3.644	5.051	4.448	2.559	3.096	1.993
Number of municipios	221	53	42	37	22	40	12	19	20	76
Number of protected houses ...	258.072	81.848	57.486	51.602	36.335	54.379	25.102	58.297	37.063	186.631
Number of protected localities	7.483	2.608	2.641	3.358	2.375	2.858	824	2.721	616	9.565
Size of protected localities according to the number of houses:										
a. 1-5 houses	3.007	1.079	1.074	1.912	1.402	1.663	401	1.637	188	6.229
b. 6-10 houses	1.140	458	549	569	400	376	149	418	66	1.343
c. 11-25 houses	1.579	628	601	596	344	429	153	341	126	1.031
d. 26-50 houses	871	261	244	175	142	212	73	151	89	500
e. 51-100 houses	468	97	90	55	52	105	23	85	77	269
f. 101-500 houses	345	69	72	39	29	64	19	65	58	159
g. 500-1000 houses	39	9	5	8	1	4	3	18	8	23
h. more than 1000 houses ...	34	7	6	4	5	5	3	6	4	11
Number of localities where anophelines were found	2.279	923	1.062	1.247	610	972	491	1.095	510	3.949
Percentage of localities with vectors:										
a. *A. albimanus*	11.2	6.3	2.9	2.6	0.6	4.0	3.0	7:7	6.9	8.3
b. *A. albitarsis*	26.8	38.8	46.0	65.5	35.4	50.1	18.7	20.1	7.8	34.6

TABLE 1 (*cont.*)

Groups of municipios according to first year without indigenous cases	A (1949)	B (1950)	C (1951)	D (1952)	E (1953)	F (1954)	G (1955)	H (1956)	I (1957)	J still infected
c. *A. aquasalis*	2.8	3.0	0.4	0.6	1.0	2.0	2.2	3.6	9.4	9.8
d. *A. darlingi*	12.5	19.1	17.5	17.6	24.8	18.1	24.0	17.9	6.5	25.3
e. *A. nuñez-tovari*	0.3	0.3	0.8	0.1	0.5	4.0	7.7	7.0	44.1	23.6
f. *A. pseudopunctipennis*	42.5	43.6	35.1	13.0	25.2	10.7	35.0	24.2	21.0	10.2
Positive slides per 100.000 house visits in year of highest infection	749	1,994	1,514	898	2,826	8,259	8,683	4,952	5,488	4,269
Visits to houses by rural visitors since first year without indigenous cases or in 1955-1957	665,773	283,312	192,977	137,061	113,690	98,076	70,154	75,656	63,503	802,264
Number of outpatients in public medical dispensaries or hospitals since first year without indigenous cases or in 1955-1957	5,817,936	967,715	936,837	682,423	403,198	390,565	225,636	339,574	299,293	1,009,467
Slides examined since first year without indigenous cases or in 1955-1957	60,091	21,375	23,980	30,198	31,774	26,990	17,726	31,742	35,925	244,637
Cases of communicable diseases notified by doctors (1955-1957)	259,703	68,005	47,140	32,901	17,704	19,993	12,304	26,061	24,854	62,582
Cases of malaria notified by doctors (1955-1957)	132	109	33	52	84	138	59	320	324	1,627

TABLE 1 (*cont.*)

Groups of municipios according to first year without indigenous cases	A (1949)	B (1950)	C (1951)	D (1952)	E (1953)	F (1954)	G (1955)	H (1956)	I (1957)	J still infected
Number of cases confirmed microscopically (1955-1957) …	63	8	2	9	25	32	50	109	201	2,829
Classification of these confirmed cases:										
a. Indigenous …	0	0	0	0	0	0	0	17	106	2,327
P. vivax …	—	—	—	—	—	—	—	15	105	2,199
P. falciparum …	—	—	—	—	—	—	—	2	1	119
P. malariae …	—	—	—	—	—	—	—	—	—	1
Mixed …	—	—	—	—	—	—	—	—	—	8
b. Imported …	54	8	2	4	24	32	49	92	95	496
P. vivax …	50	7	2	4	24	32	48	82	85	449
P. falciparum …	3	—	—	—	—	—	1	9	9	44
P. malariae …	1	1	—	—	—	—	—	—	—	1
Mixed …	—	—	—	—	—	—	—	1	1	2
c. Introduced …	0	0	0	3	0	0	0	0	0	0
P. vivax …	—	—	—	3	—	—	—	—	—	—
d. Induced …	8	0	0	1	0	0	1	0	0	6
P. vivax …	3	—	—	—	—	—	1	—	—	4
P. malariae …	5	—	—	1	—	—	—	—	—	2
e. Sporadic …	1	0	0	1	1	0	0	0	0	0
P. vivax …	—	—	—	1	—	—	—	—	—	—
P. malariae …	1	—	—	—	1	—	—	—	—	—
Number of sprayings per house to reach first year without indigenous cases …	3.6	3.5	4.7	4.8	6.4	7.4	6.4	10.2	13.5	14.4

genous cases, only 119, or 5.1 per cent, were due to that parasite. Of the 39 localities where this parasite was found in 1957, 38 were less than 50 kms. from the borders, what indicates the influence of imported infections. In the infected sector of North-Eastern Venezuela, surrounded by the eradication area, no slids with *P. falciparum* were found in the last three years.

Of the 9,565 protected localities in the 76 municipios still infected only 346, or 0.4 per cent, gave cases in 1957, and, of these, 205 or 59 per cent gave one case each, what probably indicates that transmission is vanishing. In the 104,646 inhabitants of these 346 localities, which represent 8.4 per cent of the whole population of those municipios, were found only 785 indigenous cases that year, or 845 cases per 100,000 persons, a very low figure indeed. Several causes seem responsible for persistence of malaria in this area:

(1) *Residual foci* — Due mostly to delayed spraying cycles or to houses left without spraying. In a large program some delays are frequently unavoidable, and transmission can take place in Venezuela from the fifth month of the spraying (Gabaldon, 1951). Also, in sectors to where people are moving, new houses are built after the spraying squads go over so that they may remain several months without the insecticide. To eliminate this factor additional work has been undertaken; so that each new house receive treatment as soon as finished. These residual foci (see Table 2) gave 49.1 per cent of the indigenous cases found in the last three years, and have decreased as follows: 229 in 1955 with 522 cases, 207 in 1956 with 430 cases, and 146 in 1957 with 354 cases, what indicates that with perfection of work they will finally be eliminated. Some of the houses left without spraying are due to unknown Indian tribes scattered in the forests. Surveys from planes will be required to overcome this problem. Near the borders these foci are maintained by imported cases, because of the 243 infections found in 1957 in these sectors, 24 or 10 per cent came from abroad, while in localities of this area situated more than 100 kms. from the border no imported cases were found.

The area occupied by these residual foci is the largest still with malaria (Table 2), representing 83.4 per cent of the infected territory in 1957. It has one infected locality for each 1083 sq. kms. and 54 indigenous cases per 100,000 inhabitantes. The predominant anophelines of the vectorial fauna indicate that *A. darlingi* and *A. albimanus* are

TABLE 2 — *Venezuela: 1957 data of the area still infected that year (Group J of municipios in Table 1)*

Data	Residual foci	Partially refractory malaria	
		East	West
Number of municipios	32	4	40
Area (sq. km.)	159,160	1,970	29,804
Population (July 1st., 1957)	661,600	46,300	220,200
Number of protected localities	5,342	343	3,947
Number of infected localities	147	47	152
Percentage of infected localities	2.8	13.7	3.8
Population of infected localities	46,855	10,227	47,564
Percentage of infected localities with only one case	55.8	40.4	10.5
Slides examined	68,361	12,880	83,008
Indigenous cases	354	162	269
Other types of cases	29	0	29
Localities originally found with anophelines	2,245	133	1,541
Percentage of these localities with:			
A. albimanus	11.2	15.0	2.6
A. aquasalis	11.4	49.6	3.1
A. darlingi	36.9	0	10.4
A. nuñez-tovari	0.3	0	59.6

the main responsible species. *A. aquasalis* in the infected localities of this area belong to deme IV of Senior-White (1953). That fauna has always given responsive malaria to insecticides and is entirely different from the one found in the other two areas of partially refractory malaria (Table 2).

(2) *Partially refractory malaria in Eastern Venezuela* — Partial natural refractoriness of malaria is due to out-of-doors transmission characteristically produced by some anopheline species which, being indoor-biters and resters and outdoor-biters and resters, allow the possibility of remaining cases after indoor transmission has been eliminated by the residual insecticide (Gabaldon, 1953). In Eastern Venezuela there is a small area where *A. aquasalis* with eggs of the *emilianus* type is the responsible vector. It belongs to a special group, deme III of Senior--White (1953) which, biting and resting out-of-doors, has kept some transmission in spite of 2.3 sprayings per year received as an average by the localities of the area since 1950 (Table 2). The area with this

problem is very small: it represents 1 per cent of the territory still infected and has 4.8 per cent of its population. In 1957 it gave 20.6 per cent of the indigenous cases found in the country, with an indigenous morbidity rate of 350 per 100,000 inhabitants, which is seven times the rate of the area with residual foci. When this small area become finally eliminated the only remaining infected zone of Venezuela will be near the borders.

(3) *Partially refractory malaria in Western Venezuela* — Here is found another area which has continued to give cases, in spite of an average of 2.0 sprayings per year and locality since 1950. The predominant vector is *A. nuñez-tovari,* practically absent from the other two areas under discussion (Table 2). This mosquito is less sturdy than *A. aquasalis* and has kept transmission only in sectors where the houses are near the forest or in banana plantations, where particular ecological conditions allow the anopheline to live long enough to let the parasite reach the sporozoite stage. In neighbouring areas, with pastures or annual crops of small plants, transmission has been interrupted by the insecticide. Due to this fact there is here less malaria than in the *aquasalis* area mentioned above. In 1957 the region under consideration gave 34.3 per cent of the indigenous cases of the country, but represents only 15.6 per cent of the territory and 23.7 of the population of the area still infected. The indigenous malaria morbidity rate was that year 122 per 100,000 or twice as much as in the area with residual foci.

DISCUSSION

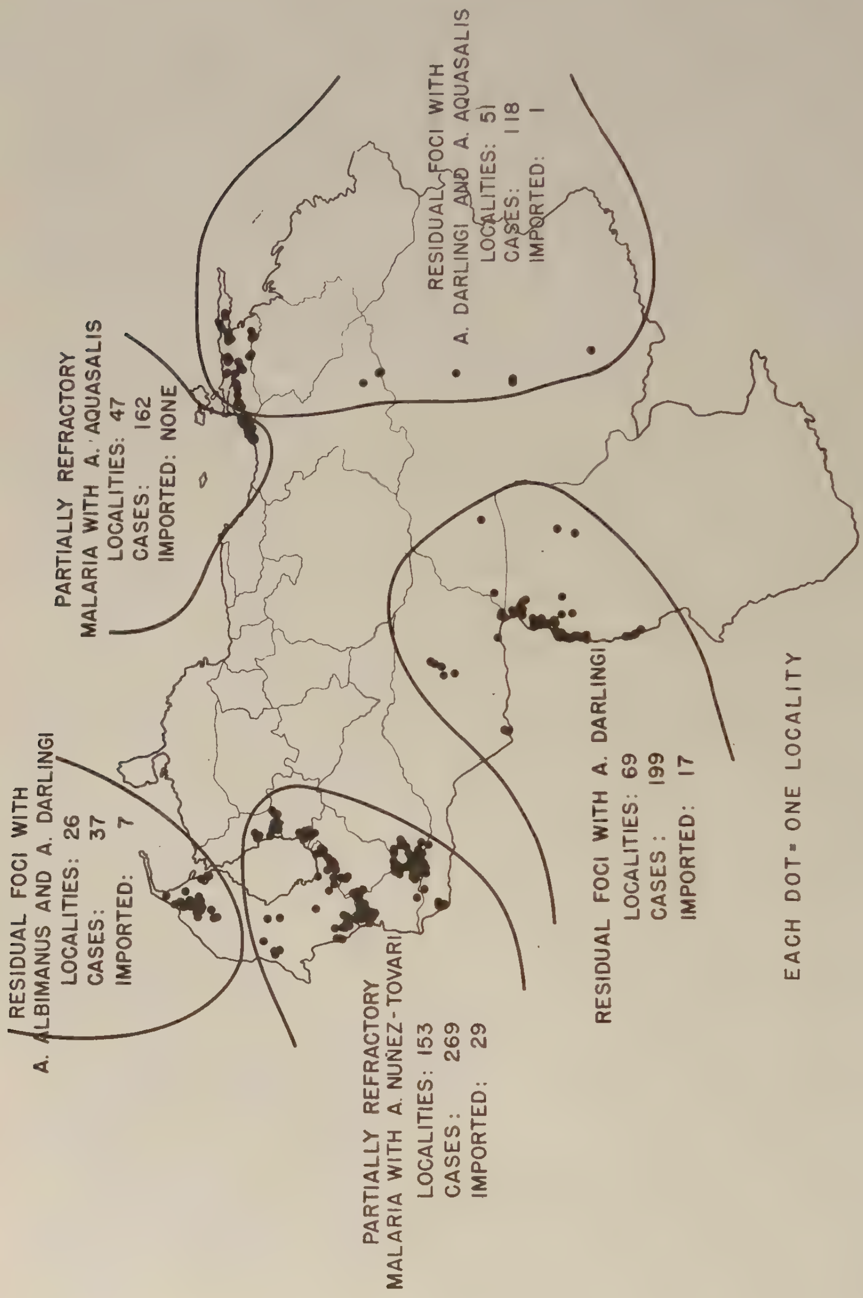
Of the four phases of a malaria eradication program, the first, or preparatory, was mostly carried out before DDT appeared, as our service had started work in 1936. The second, or attack phase, was operated under an expansive way as stated above. This fact, and the dissimilar degrees of endemicity and epidemicity of the municipios (Gabaldon, 1956), were responsible for the progressive increase in size of the eradicated areas since 1949 (Table 1).

The third, or consolidation phase, has not differed in the Venezuelan program from the attack phase, as spraying was continued during the first three years without indigenous cases. It was not known then that those were going to be the first years without the infection. The discovery of any non-indigenous case is followed by what has been called «the fire-fighting technique», or re-spraying of the infected locality and neighbouring one in a radius of 5 km if the insecticide is older than three months, and intense search for malaria parasites at the moment of the finding and every four weeks for several months afterwards. Positive cases were treated first with only chloroquine and later with chloroquine and primaquine. If in this search one or more indigenous cases were found the whole municipio was transferred to the infected group. This has happened in two occasions after arrival of imported cases, one of them due to accidentally delayed spraying, and the other to new houses after spraying (Gabaldon, Berti and Lopez, 1956).

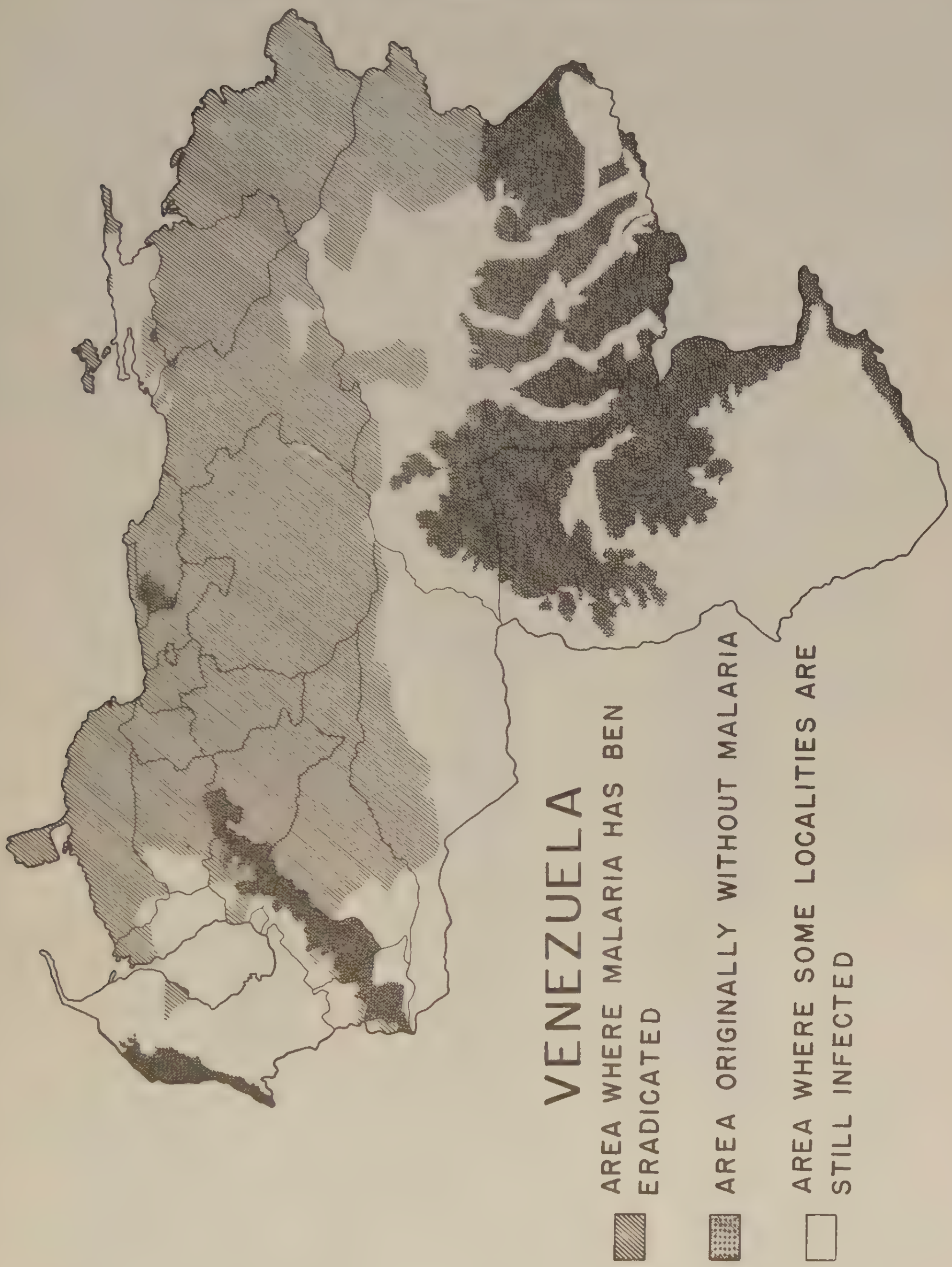
During the fourth, or maintenance phase, the antimalaria service has been transformed into a triatomid control organization with dieldrin house spraying. A number of municipios or large parts of them have been, however, left without any spraying at all during this phase due to absence of triatomids or to lack of funds. In the last three years the area left without insecticide has increased from 57,120 sq. kms. with a population of 446,500 in 1955 to 157,226 sq. kms. with a population of 1,092,000 in 1957.

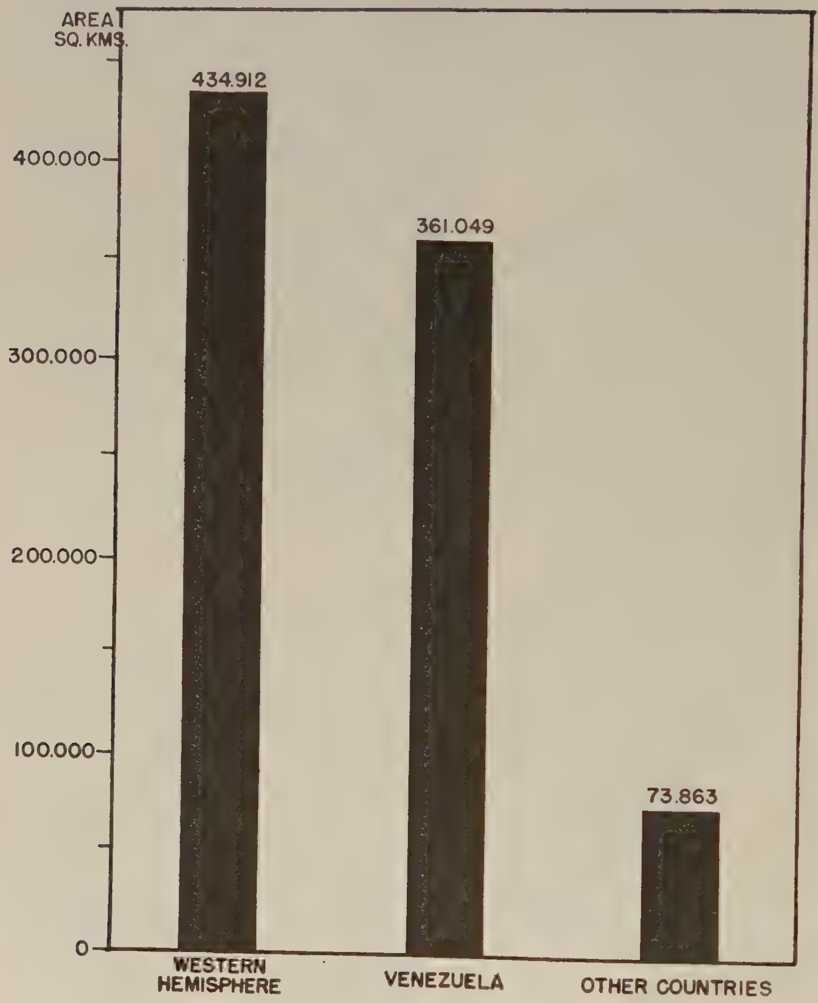
Eradication of malaria from a large area of Venezuela, that is, the absence of indigenous cases from that area for at least three consecutive years, seem a fact to be clearly established. In seven groups of municipios (A to G in Table 1) absence of disease has been from nine to three years. The proof of this absence is based in the clinical search for malaria in 9,424,310 out-patients going to medical dispensaries and hospitals, in 1,561,043 house visits by rural visitors, and in the examination of 212,134 blood thick-films taken mostly to suspected persons of both groups. In the last three years (1955-1957), only 189 cases were found with malaria parasites in these municipios. Of these cases, 173 were imported, three introduced, 10 induced and three sporadic. In the area originally without malaria, and therefore not sprayed, during that time were found 61 infections, of which 56 imported and five induced. This shows that the non-indigenous cases found in the area where malaria has been eradicated can be considered normal for this time in Venezuela.

The Venezuelan program, in spite of having reached practically total coverage of the spraying since 1950, has however not ended in complete eradication of malaria from the whole country (municipios of group J


RESIDUAL FOCI WITH
A. ALBIMANUS AND A. DARLINGI
LOCALITIES: 26
CASES: 37
IMPORTED: 7
PARTIALLY REFRACTORY
MALARIA WITH A. NUÑEZ-TOVARI
LOCALITIES: 153
CASES: 269
IMPORTED: 29
PARTIALLY REFRACTORY
MALARIA WITH A. AQUASALIS
LOCALITIES: 47
CASES: 162
IMPORTED: NONE
RESIDUAL FOCI WITH
A. DARLINGI AND A. AQUASALIS
LOCALITIES: 51
CASES: 118
IMPORTED: 1
RESIDUAL FOCI WITH A. DARLINGI
LOCALITIES: 69
CASES: 199
IMPORTED: 17
EACH DOT = ONE LOCALITY

SITUATION OF MALARIA IN VENEZUELA IN 1957


VENEZUELA
▨ AREA WHERE MALARIA HAS BEN ERADICATED
▩ AREA ORIGINALLY WITHOUT MALARIA
☐ AREA WHERE SOME LOCALITIES ARE STILL INFECTED



SIZE IN 1956 (SQ. KMS.) OF MALARIA ERADICATED AREAS IN THE WESTERN HEMISPHERE EXCEPTING THE UNITED STATES OF AMERICA in Table 1). In 1957 the largest area still infected had 147 residual foci of which 86 or 58 per cent were less than 100 kms. from the borders. It seems, therefore, that eradication of malaria from Venezuela will depend, at least in part, from eradication of the disease from neighbouring countries. And it is said at least in part, because of the existence of the two areas of partially refractory malaria, described above, where insecticides have been unable to produce full interruption of transmission. In these two areas, pyrimethamine given weekly for six months failed to finish the disease as relapses appeared after six weeks of stopping drug administration. More prolonged use of drugs will be required to reach eradication in these two areas, what is the main activity of our service at the present time.

In both areas the failure of malaria eradication is due to natural behaviouristic resistance of *A. aquasalis* and *A. nuñez-tovari,* which, *being* partially outdoor resters and biters, had enough specimens escaping from the action of the insecticide to transmit the disease. These facts are important because they represent the possibility of the maintenance of some transmission from the very beginning of the spraying program. Similar happenings may interfere with malaria eradication from the world probably more than acquired physiological resistance towards the insecticides by local vectors. Due to this account it is of fundamental importance to evaluate epidemiologically any spraying program from the very beginning in order to observe if the fall of malaria produced by adequate use of an insecticide is by *crisis* or by *lysis* (Gabaldon, 1953). If it is by crisis the disease is responsive to the chemical and will reach eradication within few years. On the other hand, if it is by lysis, malaria is partially refractory to the insecticide and eradication will need some additional action which should start as soon as possible in order to avoid cumbersome delays.

SUMMARY

Of the 21 republics in the Western Hemisphere, Venezuela was, proportionately to her territory, the one most severely hit by malaria. Of the 600,000 sq. kms. originally infected there was at the end of 1957 an area of 372,600 sq. kms. where malaria is eradicated. This represents 83 per cent of the eradicated area in the whole Western Hemisphere excluding the United States, and is the largest area of malaria eradication in the tropics. Of the one million cases per year, the average figure before the campaign, there were in 1957 only

899 known infections of which 97 were imported from abroad. So that, in spite of having reached total coverage, complete eradication from the whole country has not been obtained. This is due: (1) to an area of 159,600 sq. kms. with 147 residual foci caused by unavoidable delays of the spraying cycles, new houses built after spraying squads go over, houses of unknown Indian tribes scattered in the forests, and introduced infections; and (2) to two areas of partially refractory malaria where *A. aquasalis* or *A. nuñez-tovari* maintain some transmission because of natural behaviouristic resistance due to outdoor biting and resting. This last factor may interfere with malaria eradication from the world probably more than acquired physiological resistance.

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LA ERADICACIÓN DEL PALUDISMO EN MEXICO

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PANORAMA EPIDEMIOLÓGICO

El area malárica de la República Mexicana abarca 1.147,464 kilómetros cuadrados en donde viven un poco más de 17 millones de habitantes.

Durante el quinquenio 1950-54 el promedio anual de defunciones por paludismo fué de 23,859, lo que equivale a 84.6 defunciones por cada 100.000 habitantes.

En la República Mexicana existen 25 especies de mosquitos del género *Anopheles* y una del género *Chagasia,* de las que *Anopheles pseudopunctipennis pseudopunctipennis* y *A. albimanus* son las especies transmissoras principales.

En México solamente se han identificado *Plasmodium vivax, P. falciparum* y *P. malariae.*

Nuestras concentraciones estadisticas muestran que *P. vivax* produce el 88,3 % de las infecciones; *P. falciparum* el 4,2 %; *P. malariae* el 3,4 %; son infecciones mixtas de *vivax* y *falciparum* el 3,8 % y mixtas de *vivax* y *malariae* el 0,3 %.

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 571-577, 1959

PLANEACIÓN DEL PROGRAMA

Tres son las fases en que se ha dividido nuestra Campaña; la preparatoria, con duración de un año; la de cobertura integral con insecticides de acción prolongada, que abarcará los años de 57 a 60; y la de vigilancia epidemiológica, por el tiempo preciso.

CREACIÓN DE LA CNEP

En Noviembre de 1955 se autorizó oficialmente la creación de la Comisión Nacional para la Erradicación del Paludismo en México.

De acuerdo con los estudios epidemiológicos y las facilidades de comunicación, el área malárica de la República fué dividida en 14 zonas; cada una de estas, en un número variable de sectores y cada sector, a su vez, en cinco áreas de trabajo. El área de trabajo está servida por un equipo o brigada compuesto por cinco rociadores. La Jefatura de cada zona está al cuidado de un médico malariólogo.

PRIMEROS TRABAJOS

Constituida la CNEP, fueron objetivos fundamentales en su fase preparatoria: el Reconocimiento Epidemiológico y el Reconocimiento Geográfico.

El primero delimitó el area malárica y el segundo precisó el número y caracteristicas de las casas que deberian rociarse. También se estudiaron los costumbres de la población para determinar la utilización de recursos complementarios del rociado con el fin de lograr el cese de la transmisión.

OPERACIONES EPIDEMIOLÓGICAS DE LA FASE PREPARATÓRIA

Se visitaron 19,562 localidades situadas en regiones donde la información era deficiente o nula, con el fin de conocer sus condiciones epidemiológicas y para agruparlas posteriormente de acuerdo con caracteristicas similares. Estos estudios permitieron trazar limites más precisos del área palúdica, conociendo las localidades en donde la transmisión se efectua en periodos mayores o menores de seis meses.

Aprovechando las especies *Anopheles albimanus, A. aztecus* y *A. quadrimaculatus* existentes en el Insectario del Instituto de Salubridad y Enfermedades Tropicales de México, colonizadas antes del empleo de los insecticidas clorados, se precisaron los niveles básicos de su susceptibilidad al DDT.

Se cotejaron estos datos con los obtenidos en el campo, encontrándose valores de susceptibilidade muy altos y sensiblemente iguales en ambos grupos.

El estudio de la susceptibilidad de los anofelinos transmisores a los insecticidas que utiliza el Programa se ha constituído en actividad rutinaria del mismo y lo proprio puede decirse por lo que hace a investigaciones sobre hábitos de los transmisores y pruebas biológicas de eficacia y persistencia de los rociados.

Desde la iniciación de los trabajos de erradicación se consideró conveniente utilizar medicamentos antipalúdicos para la curación de todos los enfermos localizados.

El último de Agosto de 1957, terminada la limitación del área malárica, se dieron los primeros pasos encaminados a organizar la evaluación epidemiológica sentándose las bases técnico administrativas de su funcionamento; evaluación que esperamos alcance eficacia máxima al iniciar el Tercer Año de Cobertura Integral con insecticidas, teniendo en cuenta que el 88,3 % de nuestras infecciones son producidas por *vivax* y que si antes hubiéramos intensificado los trabajos de evaluación para cubrir el 100 % del área malárica del pais, seguramente mucho de nuestro trabajo hubiera resultado infructuoso ante el hallazgo de numerosos casos de recaídas.

Para la localización de los enfermos estamos ampliando nuestra red de notificantes activos, entendidos de que las localidades que no puedan cubrirse con este tipo de colaboradores, serán trabajados por personal de la Comisión. Actualmente contamos con 65,453 fuentes de notificación voluntaria.

Debido a las características de distribución rural de médicos, los registros de morbilidad por paludismo eran imperfectos y de cuantía insignificante. Estaban limitados a las notificaciones que se recibían de los establecimientos oficiales dependientes de la S. S. A. Actualmente dichos registros se están modificando gradual y favorablemente por las notificaciones que estamos recibiendo de colaboradores.

La mortalidad por paludismo en el año de 1957 fué sólo la tercera parte de la que se consideró como promedio anual en el quinquenio 1950-54.

OPERACIONES DE ROCIADO

Considerando que las Operaciones de Rociado son la columna vertebral del Programa de Erradicación, especial cuidado tuvimos en su organización y desarrollo.

RECONOCIMIENTO GEOGRÁFICO

En un lapso de seis meses se actualizaron los mapas geográficos que cubren una extensión de 1.147,564 km², o sea el 58 % de la superficie del Territorio Nacional; se levantaron los croquis y se dibujaron y reprodujeron copias heliográficas de 51,594 unidades de trabajo que consideramos como localidades SNEP, agrupadas en forma tal que facilitassen las operaciones desde el punto de vista del rociado. En estos croquis se localizaron mediante símbolos convencionales, 3.370,096 casas, marcándolas en el terreno, una por una, con números progressivos en cada localidad.

El 68,6 % de todas las casas resultaron ser accesibles por medio de vehículos terrestres motorizados, el 30,4 % solo empleando cabalgaduras y el 1.0 % mediante vehículos fluviales.

El reconocimiento geográfico tambien reveló que el 93 % de las casas poseían superficies rociables de acabados permeables y que la superficies unitaria a rociar era de 181 m² por casa, como promedio para toda el área malárica del pais.

PRUEBA PILOTO DE ROCIADO

Para conocer el rendimiento individual de los rociadores en el trabajo, la forma en que funcionaban los equipos y el costo de las operaciones, durante los meses de Septiembre a Noviembre de 1956, llevamos al cabo una prueba piloto de rociado, de alcance nacioal.

Durante la experiencia se rociaron 7,009, localidades con 465,146 casas, obteniendo rendimientos variables según el tipo de brigada; el promedio general fué de 8.6 casas hombre dia.

COBERTURA INTEGRAL
(1957)

El año de 1957, primero de la Cobertura Integral, se rociaron 3.016,730 casas. De estas, 2.338,004 casas fueron rociadas dos veces en el año por haber utilizado DDT y sólo 678,726 fueron rociadas una vez con Dieldrin.

El mismo 1957 fueron protegidas 383,446 casas indirectamente por medio de barreras de casas rociadas en ciudades con francas caracteristicas urbanas, en donde los estudios epidemiológicos asi lo aconsejaron. Ei total de casas protegidas, que son todas las ubicadas dentro del área malárica, incluyendo las rociadas y las no rociadas pero que están dentro de las barreras, ascendía a la cantidad de 3.400,196, en las que vivían 15.587,528 habitantes.

En 1957 el total de rociamientos fué de 5.120,701, consumiéndose en esta operación 2.259,607 kg. de DDT y 134,010 kg. de Dieldrin.

El personal de campo empleado en los trabajos estuvo formado por 3,184 hombres agrupados en 115 sectores y éstos a su vez en 540 brigadas. El número de rociadores fué de 2,286 que produjeron un rendimiento promedio general de 9.6 casas rociadas por hombre dia.

El 15 de diciembre de 1957 terminó el Primer Año de Cobertura Integral. El segundo se inició, de acuerdo con Programa pre-establecido, el 2 de Enero de 1958.

COBERTURA INTEGRAL
(1958)

En el presente año el rociamiento de las casas se ha mantenido rigurosamente dentro de los lineamientos de trabajo previamente marcados en cuando a técnica y periodicidad.

El número de casas a rociar ha aumentado por diversas razones. Se estima que al finalizar el presente ejercicio se tendrá un incremento de casi un cuarto de millón de casas en relación con el año anterior.

Para el proprio 1958, las casas protegidas, incluyendo las ubicadas dentro de las barreras, alcanzarán la cifra de 3.650.000 en las que viven un poco más de 17.000,000 de habitantes.

En el presente ejercicio aumentó a 1.140,00 el número de casas a rociar con Dieldrin. La suma de rociamientos será de cerca de 5.250,000 y e se espera consumir 2.740,000 kg. de DDT y 317,000 kg. de Dieldrin.

El personal de campo ha mejorado sus redimientos. Durante el Primer Semestre del presente año se obtuvo un rendimiento promedio general de 10.23 casas rociadas por hombre dia. Esta circunstancia y el mayor empleo de Dieldrin, permitirán reducir el personal de campo en el Segundo Semestre, a pesar del aumento de casas. Actualmente laboran como promedio diario 2,764 trabajadores de campo agrupados en 475 brigadas dentro de 105 sectores. De aquéllos, más de 2,000 tienen categoria de rociadores.

LOGÍSTICA

Para asegurar la continuidad de los trabajos sin interrupción de itinerarios que tienen calendarios fijos en su desarrollo, ha sido menester contar con una organización eficiente que garantice el abastecimiento oportuno de toda clase de materiales. Se mira la importancia del control y del mantenimiento de los vehículos y semovientes. De aquellos son 645 motorizados terrestres y 10 embarcaciones fluviales; y de estos 1550 animales de monta y carga.

De fines de 1955 a Junio inclusive del año en curso, los vehículos motorizados terrestres han recorrido más de 25.000,000 de km.

EDUCACIÓN HIGIÉNICA

Desde el punto de vista de la Educación Sanitaria, tomando en cuenta la celeridad con que se desarrolla el programa, en cada comunidad se trabaja con la organización y la cultura que actualmente posee, para lograr su colaboración activa.

Interés especial acreditó la coordinación con Instituciones Oficiales, semi-Oficiales y privadas conectadas con actividades de Salud pública, para obtener su colaboración en favor de la acción educativa.

Especial atención han recibido las pequeñas localidades carentes de servicios médicos, en donde se ha logrado obtener la ayuda de los lideres de la comunidad, entre los que destacan los maestros de escuela, a quienes se designa Auxiliares Honorarios de Educación Higiénica. Hasta el mes de Junio del año en curso tenyamos 23,388 de éstos.

ADIESTRAMIENTO

La CNEP no utiliza los servicios de ninguna persona si previamente no ha recibido el adiestramiento adecuado.

Periódicamente realizamos cursos de Malariología para nuestro personal y para el que necestan algunos programas del Continente Americano. El readiestramiento en servicio es actividad rutinaria en todas las zonas.

Desde el mes de Septiembre de 1955 en que se organizó el primer curso hasta el mes de Junio del presente año, hemos adiestrado un total de 11,537 personas contando a nacionales e internacionales.

MISSÃO PERMANENTE DE ESTUDO E COMBATE DE ENDEMIAS
DE CABO VERDE
(Chefe da Missão: Dr. MANUEL T. V. DE MEIRA)

L'ERADICATION DU PALUDISME DANS L'ÎLE DE S. VICENTE (ARCHIPEL DU CAP VERT)

MANUEL T. V. DE MEIRA

I — INTRODUCTION

Le paludisme constitue le problème essentiel de la Santé Publique au Cap Vert.

Les registres du Service de Santé de la Province rélèvent 11 324 cas de malades annuellement (moyenne de 1945 à 1954); cependant le chifre réel des impaludés est sans doute beaucoup plus grand et doit atteindre, à la lumière des enquêtes récentes, environ 50 % de la population insulaire, qui comprend en tout 150 000 âmes. Selon le même Service de Santé le nombre annuel moyen de morts par malaria fût de 279 entre 1945 et 1954.

Les espèces de parasites les plus fréquentes sont *Plasmodium vivax* et *P. falciparum; P. malariae* apparaît aussi mais plus rarement.

Dans toutes les îles le seul vecteur est *Anopheles gambiae*.

Aucune lutte n'avait été organisée contre l'endémie avant 1948. Cette année-là une mission de l'Institut de Médecine Tropicale de Lisbonne entreprit dans l'île du *Sal* une campagne contre *A. gambiae* et autres culicides (*Aedes aegypti, Aedes caspius*), obtenant, dès 1950, l'éradication complète de ces espèces (3).

En 1952-53 une autre mission du même Institut est envoyée dans l'île de *S. Vicente* pour combattre la plus grande épidémie que l'île ait jamais connue dans son histoire. En 1954-55 la même mission tente l'éradication de l'endémie. À partir de Novembre 1955 l'actuelle Mission

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Permanente d'Étude et Combat des Endémies continue les travaux de surveillance, qui connaissent un plein succès, puis qu'à partir de 1954 aucun cas autochtone de malaria n'a été enregistré, bien que depuis Mars 1955 aucune mesure offensive n'est été pratiquée contre *A. gambiae,* qui a persisté dans certaines zones de l'île.

Actuellement la Mission Permanente poursuit la même lutte dans d'autres îles de l'Archipel.

Nous exposerons seulement dans ce travail la campagne qui a été realisée à *S. Vicente.*

II — DESCRIPTION DE L'ÎLE

S. Vicente est une des dix îles de l'Archipel du Cap Vert, située en plein zone intertropical.

L'île mesure 227 km², avec une longueur maximum de 24 250 km sur une largeur maximum de 16 250 km. Elle est de nature volcanique et constituée dans sa plus grande partie par des roches basaltiques et des formations calcaires. Ses principaux sommets ne dépassent pas 725 m. Le sol est aride et la végétation du type *Deserta*. Les rivières sont temporaires, ne coulant qu'à l'époque des pluies. Le climat de l'île est chaud, régulier et sec. Dans le tableau 1 nous donnons les caractéristiques météorologiques de la cité du Mindelo.

Il y a deux saisons: une fraîche, de Décembre à Mars, et une chaude, de Juillet à Novembre; entre les deux se situe une période de transition, d'Avril à Juin. Les mois les plus pluvieux sont normalement Août, Septembre et Octobre.

L'insolation totale moyenne est de 2 989 heures, soit 67 % (1945--1954).

La population de l'île en 1950 était de 19 000 habitants, dont 8 381 hommes et 10 585 femmes. Elle est actuellement de 22 000 âmes, constituée à majeur partie par des éléments indigènes, métis et noirs, et d'environ une centaine d'européens, portugais pour la plupart.

Le principal centre habité est la cité de *Mindelo,* située sur la baie de *Porto Grande,* dont la position géographique est exceptionnelle, car, située à mi-chemin entre l'Europe et l'Amérique du Sud, y s'arrètent de nombreux bateaux. Il existe dans l'île d'autres aglomérations, mais bien

TABLEAU 1 — *Élements metéorologiques du Mindelo (Île de S. Vicente)*

TEMPÉRATURE (° C)	
Moyenne annuelle	23,58
Moyenne du mois plus chaud	25,38 (IX)
Moyenne du mois plus froid	21,17 (II)
Moyenne des maxima	27,02 (1947)
Moyenne des minima	21,49 (1947)
Maximum absolu	29,7 (X)
Minimum absolu	16,5 (II)
HUMIDITÉ RELATIVE (%)	
Moyenne annuelle	69,7
Moyenne du mois plus humide	74,0 (IX)
Moyenne du mois plus sec	66,7 (I-II)
PLUVIOSITÉ	
Hauteur (m/m) moyen	132,5 (1931 à 1957)
Nombre de jours moyen	9 (» » »)

plus petites, situées à peu près toujours sur la côte et dont le nombre total d'habitants ne dépasse pas le millier.

Le trafique important que présente le port de Mindelo, principal centre urbain de la province et seul grand port de l'Archipel, augmentait les chances de persistence de l'endémie malarique, surtout si l'on considère la migration incessante de travailleurs capverdiens revenant des îles de *S. Tomé* et *Príncipe,* foyers hautemant contaminés.

III — LE PALUDISME À S. VICENTE AVANT 1953

Les Services de Santé locaux enregistrèrent, entre 1934 et 1953, un total de 30 018 cas de paludisme, soit une moyenne annuelle de 1 500 environ, avec un maximum de 3 323 en 1952 et un minimum de 362 en 1947. La moyenne annuelle d'accès pernicieux, enregistrée en 11 ans, fut de 17. En 16 ans le nombre de morts a été de 384, soit une moyenne annuelle de 24 par an. Il n'est pas fait mention dans cette statistique de la fièvre bilieuse hémoglobinurique, dont la présence ne semble pas avoir été constatée avec certitude à *S. Vicente.*

Cruz Ferreira (2) rapporte 61 cas de primo-infection palustre en 1941, et 224 en 1942, chez des soldats des troupes expéditionnaires stationnées dans l'île. Les parasites appartenaient aux espèces *vivax* (93 %), *falciparum* (5 %) et *malariae* (2 %).

En 1951 Cambournac et Meira (1), dans une enquête épidémiologique, notent dans l'île un index splénique égal à 5,2, mais ils n'observent aucune préparation positive sur 111 frottis de sang.

Meira (4), en 1952-53, au cours d'une poussée épidémique, observe 3 131 cas de maladie, dont 2 193 à *P. vivax*, 885 à *P. falciparum* et 53 infections mixtes.

IV — LE VECTEUR

Deux espèces anophéliennes existent dans l'île: *A. gambiae* et *A. pretoriensis*, mais seule la première est responsable de la transmission.

Normalement les gîtes sont representés par les puits et les étangs, dont plus d'un millier existent dans l'île. Ils peuvent aussi se trouver dans les cîternes, rigoles ou autres recipients de différents types. Durant et après les pluies les developpements larvaires se font en très grande abondance en toutes les collections d'eau formées dans le sol.

L'espèce *A. gambiae* est très domestique et se nourrit à l'intérieur des maisons.

L'indice sporozoïtique observé au cours de l'épidémie de 1952-53 atteignait 10,7.

V — LA CAMPAGNE D'ÉRADICATION

Après l'enquête biologique préliminaire nous avons entrepris la lutte le 16 Décembre 1952. De cette date à Juin 1953 on procéda à une première aplication domiciliaire de D. D. T. dans toute l'île, étendue aux abris des animaux. On utilisa le «D. D. T. téchnique», en émulsion à 5 %, et aussi le «D. D. T. mouillable» à 50 %, pulvérisés à raison d'environ 2 g/m². Le nombre de maisons ainsi traitées fut 4 041 représentant 11 889 pièces, soit une superficie totale de murs et plafonds d'environ 840 000 m². Simultanément toutes les collections d'eau permanentes furent ensemensées en gambusies venues de métropole. La population reçut aussi très largement des médicaments anti-paludiques, distribués non seulement par la Mission mais aussi par le Service de Santé local.

Afin de dépister activement les cas, nous avons fait dans les derniers mois de 1954 une première enquête malariométrique. Dans un groupe de 1 839 enfants, âgés de 2 à 15 ans, nous avons constaté une splénomégalie dans cinq cas, et une parasitémie (*P. vivax*) de 13 cas; tous ces individus avaient sans doute contracté la maladie pendant l'épidémie de 1952-53. Dans un autre groupe de 72 enfants âgés de moins de 2 ans, l'enquête fut absolument négative. Les autres examens clinique et parasitaires faits sur notre initiative ou à la demande, et qui portent sur quelques centaines de tout âge, donnèrent aussi des résultats absolument négatifs.

En Novembre 1954, comme *A. gambiae* persistait dans certaines zones de l'île, et que rentraient de nombreux porteurs de germes venant de S. Tomé et du Principe, nous avons entrepris une seconde application de D. D. T., suivant la même méthode de la première fois. En même temps la lutte anti-larvaire au moyen de pétrole fut effectuée dans tous les gîtes existants dans l'île. Cette seconde opération offensive se termina le 10 Mars 1955, date qui correspond à la fin de la phase d'attaque.

Après la venue dans la province de l'actuelle Mission Permanente, le 1^er^ Novembre 1955, notre action s'est limitée à une surveillance active dans le but de dépister tous nouveaux cas ou des foyers résiduels; de plus, nous avons effectué le contrôle parasitologique des «importateurs» de maladie, ceci en raison de la persistence de quelques vecteurs en quelques coins de l'île. Dans ce but nous avons effectué des enquêtes répétées chez les enfants et les adultes, qui couvrirent une grande partie de la population de l'île et dont les résultats demeurèrent toujours négatifs. En même temps nous avons intensifié la surveillance et le traitement des travailleurs capverdiens revenant de *S. Tomé* et du *Principe*, dont un grand nombre sont impaludés: 3 000 environ revinrent dans l'île durant les années 1956 et 1957.

En conclusion, on peut considérer que le paludisme a été éradiqué de l'île de *S. Vicente* depuis Mars 1957, c'est à dire, trois ans et trois mois justes après la disparition dans l'île de nouveaux cas de maladie et exactement deux ans après la cessation de toute méthode offensive. Cette bonne situation se mantient à l'heure actuelle — 18 Avril 1958. Dans le but d'obtenir une solution définitive, la Mission va entreprendre de nouveau la lutte contre *A. gambiae,* ayant pour objectif l'éradication du vecteur.

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ERADICATION DU PALUDISME ET RESISTANCE DU VECTEUR AU D. D. T., AU PORTUGAL

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I — INTRODUCTION

Jusqu'à présent, on ne peut citer un seul exemple de campagne d'éradication du paludisme de large envergure, compromise en raison du développement, chez les vecteurs, d'une résistance aux insecticides. En effet, si l'on passe en revue les études des dernières années, on arrive vite à la conclusion que la résistance du type dit physiologique, c'est-à-dire consécutive à des contacts prolongés, avec un insecticide quelconque, constitue pour l'instant un phénomène rare, et que là même où l'existence de souches résistantes a été constatée leur aire de dispersion reste limitée.

Cependant, étant donné qu'il serait contraire à l'esprit scientifique d'espérer que cet état de chose se maintienne encore longtemps, puisqu'il s'agit d'une situation tout à fait exceptionnelle chez les nombreux insectes nocifs, tant pour la santé publique que pour l'agriculture, il faut considérer comme très opportune la résolution adoptée à la Huitième Assemblée Mondiale de la Santé, en 1955, d'inviter «les gouvernements à intensifier leurs programmes nationaux de lutte antipaludique, afin que l'éradication puisse être réalisée et que des campagnes de pulvérisations d'insecticides puissent être arrêtées à coup sûr, avant que ne se manifeste le danger possible d'une résistance aux insecticides chez les espèces anophéliennes vectrices».

Dans une récente étude de l'Organisation Mondiale de la Santé (1), on résume ainsi les résultats des épreuves de sensibilité en appliquant la méthode bien connue de Busvine et Nash (2) sur de multiples espèces anophéliennes: «à quelques exceptions près, dans les parties du monde où

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ces tests ont eu lieu, la L. C. 50 du D. D. T., pour les moustiques anophèles non soumis à une pression d'insecticide, varie entre 0,5 % et 1,5 %». Dans un récent article (3), Raffaele et Coluzzi (1957) ont attiré l'attention sur le fait que les taux de mortalité vérifiés dans le groupe maculipennis, y compris l' *A. atroparvus,* en Italie, présentent des valeurs très basses pour le D. D. T., ce qui revient à dire que les limites des L. C. 50 correspondantes sont considérablement plus élevées. Nous verrons que nos études nous ont conduit aux mêmes conclusions, en ce qui concerne l'*A. atroparvus* au Portugal.

Dans la communication non publiée que nous avons faite à la Conférence sur le Paludisme de l'Organisation Mondiale de la Santé, réalisée à Athènes en 1956, nous avons signalé la culture rizicole et le mouvement migratoire qui en dépend-considérablement accrus au cours des dernières années-comme étant le facteur le plus important ayant entravé la lutte pour l'éradication du paludisme en Portugal continental.

Le but de notre exposé étant d'attirer votre attention sur l'intervention d'un autre facteur, laissé de côté jusqu'ici, nous voudrions, avant de rapporter les résultats de nos nouvelles constatations, donner quelques renseignements sur l'épidémiologie de l'infection au Portugal et sur l'orientation adoptée au début des opérations.

L'endémie se trouvait autrefois répartie dans le pays en cinq zones, classifiées par Cambournac (1942) (4), selon les conditions climatiques: région littorale du Nord, région littorale du Centre, région littorale du Sud, région continentale du Nord et région continentale do Sud.

Dans les régions littorales, où l'humidité relative est très élevée, l'anophélisme est très intense; il l'est beaucoup moins dans les régions continentales, plus sèches.

On trouve l'anophélisme partout, même aux hautes altitudes (1.800 m); un seul secteur (*A. atroparvus*), avec des tendances zoophiles accentuées et un endophilisme marqué.

En ce qui concerne les types d'infection, on a toujours constaté uneprédominance très nette des infections à *P. vivax* dans les régions du nord, et parfois du *P. falciparum* au sud, notamment dans certaines localités situées dans la vallée du Sado. On ne trouve que rarement des infections à *P. malariae,* excepté dans la région littorale du nord.

Quelques chiffres permettront de se faire une idée de l'incidence du paludisme dans le temps: pendant la dernière guerre, le nombre de cas décelés chaque année s'élevait à près de 70.000, en 1943 l'examen fut positif pour 41.003 cas et il y eut 435 décès; après la guerre, l'endémie commença à décliner rapidement et en 1948, année précédant le début de la campagne actuelle, le nombre de cas positifs n'était plus que de 15.200 et celui des décès de 63.

En 1948, lors de la disparition prématurée du regretté paludologue F. Landeiro, nous fûmes chargé d'élaborer un plan de campagne à l'échelle nationale, pour aboutir à l'extinction rapide de l'endémie au moyen d'insecticides à effet rémanent. On pouvait alors espérer qu'aucune difficulté ne viendrait entraver la réalisation de ce plan.

En effet, les conditions locales étaient pour ainsi dire idéales: un seul vecteur à endophilisme accentué; territoire à traiter relativement restreint et possibilité d'exécuter le plan avec une grande économie de moyens, puisqu'on savait d'avance que, les sources de l'infection localisées dans les vallées du Tage et du Sado une fois taries, cet effet devrait s'étendre à d'autres régions, en particulier la région littorale du nord, où l'endémie était entretenue par le mouvement migratoire périodique dû à la culture rizicole.

Quelques renseignements encore, concernant le rytme des pulvérisations, l'époque de l'année, les insecticides choisis: une pulvérisation par an; la campagne devait se terminer au plus tard au début de Juin; le HCH serait utilisé dans la région continentale du nord et le D. D. T. dans les autres.

La lutte antilarvaire ne serait utilisée que dans certains centres urbains.

Voici, comparés aux chiffres exprimant la morbidité et la mortalité dues au paludisme pendant l'année précédant la campagne, les résultats des cinq dernieres années:

	Cas positifs (1)	Décès
1948	15.200	63
1953	608	14
1954	409	12
1955	184	8
1956	95	1
1957	43	5

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[1] Les chiffres relatifs aux cas positifs ont été fournis par la Direction des Services d'Hygiène Rurale et de Lutte Antipaludique.

II — ETUDES COMPARATIVES SUR LA SENSIBILITÉ DE *L'A. ATROPARVUS* AU D. D. T.

Les épreuves de sensibilité effectuées jusqu'à présent ont porté sur un total de 3.400 anophèles femelles, élevés à l'insectarium de l'Instituto de Malariologia.

Pour tous les essais, nous avons suivi la technique de Busvine et Nash (2), en respectant autant que possible les instructions données par les auteurs, en ce qui concerne les conditions de température et d'humidité relative. Les femelles, âgées de á à 20 jours, ont toujours été soumises à l'épreuve 24 heures après un repas de sang de lapin; la lecture de la mortalité était faite 24 heures après, sans tenir compte des femelles apparemment moribondes.

En ce qui concerne le nombre de femelles par chambre de contact, détail technique très important, on le verra, il a toujours été de six au cours des années précédentes. Cette année, nous avons également fait des essais où ce nombre était réduit à une femelle par chambre, selon la modification apportée à la méthode par Raffaele et Coluzzi (1957 (5).

Résultats de 1955 à 1957 — Dans l'impossibilité de rapporter tous les résultats, dont quelques-uns sont d'ailleurs douteux, nous nous contenterons de faire état d'une des études comparatives concernant une souche originaire d'un endroit non traité (Águas de Moura) et une autre souche provenant d'un endroit où le D. D. T. a été utilisé depuis 1949, à raison d'une pulvérisation par an.

Provenance des souches	Dose de DDT par m² correspondante à la concentration utilisée	Taux de mortalité %
Águas de Moura (non traité)	1,75 g	30 % (1956)
Foz (traité)	1,40 g	52 % (1956)

De ces résultats, l'important à retenir est évidemment cette apparente contradiction: la souche *A. Moura* a été moins sensible que celle de l'endroit traité.

Résultats relatifs à 1958 — En comparant les résultats donné souche par souche dans les tableaux qui suivent, on peut constater que la mortalité est beaucoup plus élevés dans les cas où les femelles sont exposées par groupes de six par chambre. Il faut donc considérer comme plus valables les essais où les femelles étaient exposées individuellement, car on écarte ainsi une cause de mort pas du tout négligeable, indépendante de l'action directe du toxique.

On remarquera que la souche *A. Moura* continue à se montrer moins sensible que la souche Foz et que la nouvelle souche *Alcacer,* provenant d'un endroit traité pendant plusieurs année consécutives, s'est révélée aussi sensible que la première.

TABLEAU 1 — A. atroparvus *femélles élevées en laboratoire, $1^{\text{ère}}$ progéniture, exposées 24 h. après un repas de sang,* à raison de six par chambre, *à des papiers imprègnés d'une solution de D. D. T. dans l'huile de Risella de concentration équivalente à 1,75 gr. par m^2*

Provenance des souches	Total de pulvérisations de DDT (une chaque année)	Âge en jours des femelles exposées	Nombre de femelles exposées	Mortalité 24 h. après	Taux de mortalité %
Foz (vallée du Tejo)	9	6-10	240	89	37
Alcácer (vallée du Sado)	9	7-15	120	28	23,3
A. Moura (vallée du Sado)	0	5-20	120	55	45,8

TABLEAU 2 — A. atroparvus *femélles élevées en laboratoire, $1^{\text{ère}}$ progéniture, exposées 24 h. après un repas de sang,* à raison d'une par chambre, *à des papiers imprègnés d'une solution de D. D. T. dans l'huile de Risella de concentration équivalente à 1,75 gr. par m^2*

Provenance des souches	Total de pulvérisations de DDT (une chaque année)	Âge en jours des femelles exposées	Nombre de femelles exposées	Mortalité 24 h. après	Taux de mortalité %
Foz (vallée du Tejo)	9	4-10	80	11	13,7
Alcácer (vallée du Sado)	9	5-11	160	8	5
A. Moura (vallée du Sado)	0	4-11	120	6	5

Note — La concentration léthale moyenne (CL$_{50}$) n'a pu être utilisée comme élément comparatif, du fait que la solubilité maximum du D. D. T. dans l'huile de Risela est de 5 %. En ce qui concerne les taux de mortalité chez les témoins, on informe qu'ils sont négligeables.

III — INTERPRÉTATION DES RÉSULTATS

Le nombre d'études publiées concernant l'influence exercée sur les résultats par certains facteurs, tels l'âge des moustiques et le moment où se déroulent les expériences par rapport au repas de sang, est insuffisant pour servir de base à des notions précises. Néanmoins, il est possible d'affirmer que la sensibilité des moustiques aux insecticides s'accroît avec l'âge et diminue jusqu'à 24 heures après un repas de sang. Nos expériences portant sur des femelles âgées de 4 à 20 jours, soumises au contact du D. D. T. 24 heures après un repas de sang, nous inclinent à admettre comme excellentes les conditions de leur résistance à l'action du toxique.

L'examen général des résultats rapportés, inclus à ceux des années précédentes, révèle que la souche *Foz* — provenant d'un endroit situé dans la vallée du Tage et traité pendant plusieurs années consécutives — a révélé un degré de sensibilité au D. D. T. nettement plus élevé que celui des sources *Alcacer* et *Moura* — la première provenant d'un lieu traité pendant plusieurs années consécutives; la deuxième d'un endroit non traité, situé dans la vallée du Sado.

En tenant compte des résultats que l'on doit considérer les plus valables, on vérifie que la souche *Foz* continue à se manifester plus sensible au D. D. T. que les autres et que les souches *Alcacer* et *Moura* montrent une faible sensibilité à cet insecticide et au même degré. Ces faits nous permettent donc d'exclure l'éventualité la plus redoutable et nous conduisent à accepter les résultats relatifs aux souches *Alcacer* et *Moura* comme représentant leur sensibilité normale au D. D. T.

Il est fort possible que, dans la plupart des régions du pays, les niveaux de sensibilité normale du vecteur à l'égard de cet insecticide ne soient pas si bas. Cependant n'oublions pas que la vallée du Sado a toujours été l'épicentre de l'endémie et — pour reprendre les paroles de Miscsiroli à propos des difficultés de l'éradication de l'*A. labranchiae* en Sardaigne — le «centre génétique» du vecteur. C'est donc là, en cas de poussée d'épidémie, si petite soit-elle, que l'on devra redouter le plus les effets.

L'éxamen de la courbe des cas positifs de la campagne en cours nous indique une baisse d'une année à l'autre d'environ 50 % sur l'année précédente. Cette marche régressive, lente et régulière, dénonce évidemment l'intervention d'un facteur de nature permanente.

Les faits énoncés semblent donc nous permettre d'affirmer — tout en attachant aux facteurs rizières et mouvements migratoires qui en découlent, leur rôle prédominant — que le faible degré de sensibilité normale du vecteur au D. D. T. — insecticide le plus utilisé dans la campagne en cours — constaté dans la vallée du Sado, jadis, foyer principal de l'endémie, a sensiblement contribué à retarder l'acheminement de l'éradication du paludisme au Portugal continental.

IV — CONCLUSIONS

1 — Les recherches effectuées, de 1956 à nos jours, pour déterminer la sensibilité normale du vecteur (*A. atroparvus*) au D. D. T., qui ont porté sur un total de 3.400 anophèles femelles élevées à àl'insectarium de l'Instituto de Malariologia, selon la technique ordinaire de Busvine et Nash, et aussi d'après les modifications que Raffaele et Coluzzi (1956) y apportèrent, ont montré, par les taux de mortalité vérifiés, que la sensibilité normale du vecteur à l'égard de cet insecticide est de faible intensité, du moins dans deux souches originaires de la vallée du Sado.

2 — Les résultats concordent avec ceux de Raffaele et Coluzzi (1957) sur la sensibilité normale des anophèles du groupe maculipennis, l'*A. atroparvus* y compris, en Italie.

3 — La faible sensibilité normale du vecteur, constatée sur certaines souches, nous conduit à accepter que ce facteur a contribué de façon appréciable à retarder l'acheminement de l'éradication du paludisme au Portugal Continental.

4 — Cette étude montre que la connaissance des niveaux de sensibilité normale des vecteurs aux insecticides usuels est de grande importance pour la conduite des opérations dans les campagnes d'éradication.

RESUMÉ

Au début de la campagne d'éradication du paludisme au Portugal Continental, on ne pouvait prévoir que, neuf ans plus tard, on n'aurait pas encore réussi à interrompre la transmission de l'infection sur tout le territoire, puisque les conditions locales étaient pour ainsi dire idéales: un seul vecteur *(A. atroparvus)* à endophilisme marqué et le territoire à traiter relativement restreint. L'A. rapporte les résultats des essais effectués afin d'évaluer le degré de sensibilité du vecteur au D. D. T., en utilisant la méthode ordinaire de Busvine et Nash

et la modification à cette technique apportée par Raffaele et Coluzzi, en montrant que la sensibilité normale du vecteur au D. D. T. présente des valeurs très réduites chez certaines souches originaires de la vallée du Sado, épicentre de l'endémie dans le passé. L'A. conclue que cette particularité, inconnue jusqu'alors, a contribué de façon appréciable à ralentir l'acheminement de la lutte pour l'éradication du paludisme au Portugal Continental et souligne que la présente étude est une contribution de plus pour montrer que la connaissance des niveaux de la sensibilité normale des vecteurs aux insecticides usuels est indispensable à la conduite des opérations.

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EXPERIENCES OF CEYLON'S MALARIA ERADICATION PROGRAM

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I — INTRODUCTION

1. Ceylon is a small island situated in the tropical belt lying between 5° 55′ and 9° 50′ north latitude and 79° 42′ and 81° 53′ east longitude. It is 25,332 square miles in extent. It is roughly elliptical in shape with its long axis lying north-south and being 270 miles at its greatest length along this axis, and 140 miles at its greatest breadth.

2. From historical records, it would appear that malaria existed in Ceylon at least as far back as 300 A. D., and continued its ravages unrestrained until 1947, when successful control was first achieved on a nation-wide scale.

3. Prior to the achievement of successful control, the disease was hyperendemic in three quarters of the extent of the country (map). Spleen rates in this hyperendemic area as a whole were over 60 % though a great many individual localities within this area recorded rates of 90 %-100 %.

4. The birds-eye view of this area was one of pockets of human habitations of greater or lesser extent studded within a vast jungle which surrounded them on all sides. Here man had retreated in the face of the onslaught by malaria, and the jungle had taken over the conquered territory. Once beautiful cities now lay submerged beneath the jungle, to be restored, we now know, at a later date when man was to conquer malaria.

5. In more than half of the remaining quarter of the extent of the country, malaria was of low to moderate endemicity, and this area was subject to cyclical epidemics of great severity. This area was devoid of jungle and thickly populated.

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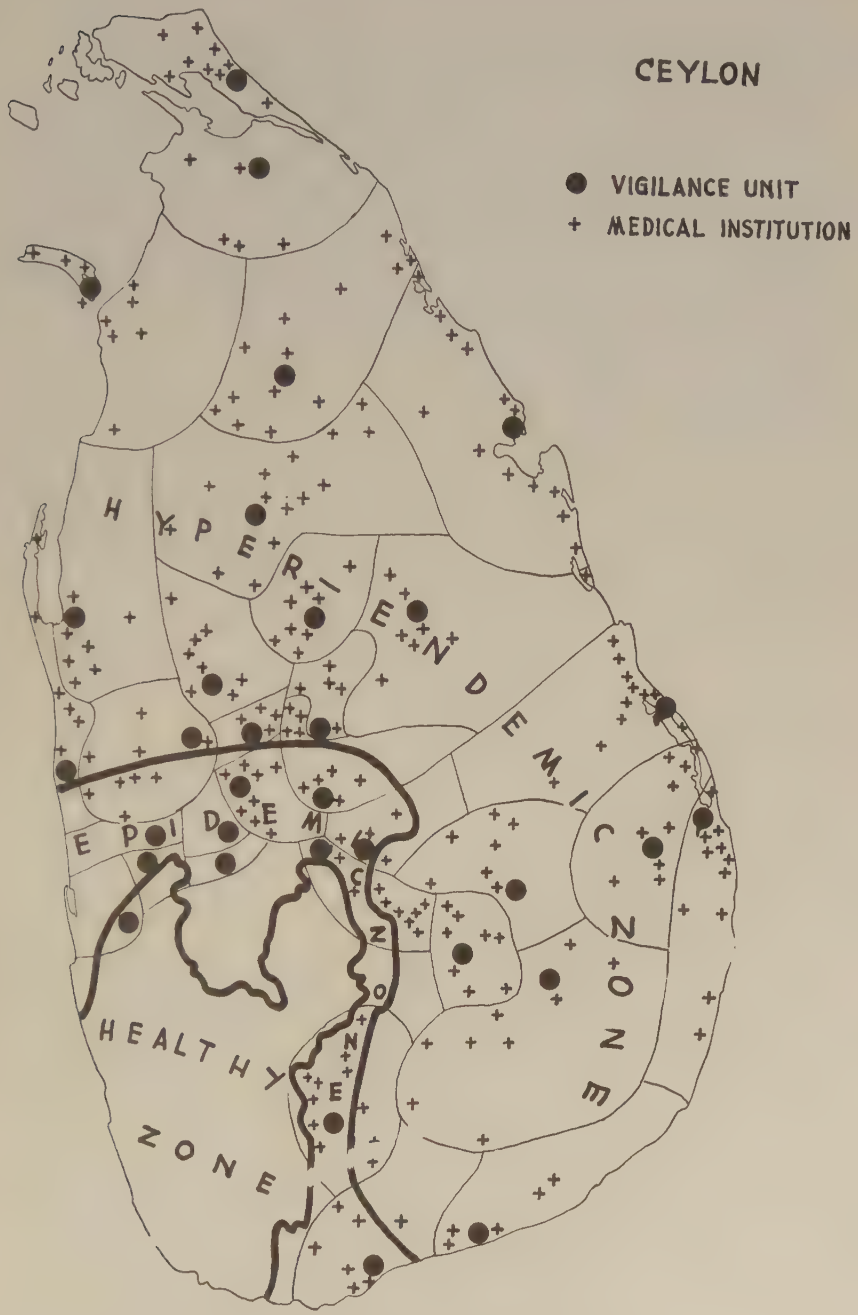
CEYLON
● VIGILANCE UNIT
+ MEDICAL INSTITUTION
HYPERENDEMIC ZONE
EPIDEMIC ZONE
HEALTHY ZONE

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6. The remaining extent of the country which was less than one-eighth of the whole, was completely free of the occurrence of malaria transmission.

7. The only vector of malaria in the country is anopheles culicifacies, which, when found in areas inhabited by man, appears to be an intensely domestic species which is both endophilic and endophagous. It is, however, found to be uniformly distributed throughout the vast jungles of the hyperendemic area of the country, far removed from human settlements and is then exophagous, exophilic and zoophilic, but ever ready to adapt its feeding and resting habits on the intrusion of man into its sanctuaries in these jungles, to become endophilic, endophagous and anthropophilic.

8. The three common species of malaria parasites, *Plasmodium vivax, Plasmodium falciparum* and *Plasmodium malariae* were found in abundance in the country, *Plasmodium malariae* being the predominant species in the hyperendemic zone, whilst the other two species were more numerous in the epidemic zone.

II — MALARIA CONTROL

1. The history of malaria control in Ceylon dates back to a period about a decade after Ross' discovery of the transmission cycle of malaria, when in 1911 malaria control measures were first instituted in an urban area in the epidemic zone. During the course of this work in 1911 the vector species was identified and so also the presence of the three species of plasmodia mentioned earlier.

2. By 1921, a full-time malariologist had been appointed and his duties included fundamental research as well as the organisation of control measures. By 1922, malaria control work had been undertaken in several urban areas and this work was progressively expanded to include more urban centres of population.

3. The great malaria epidemic of 1935 demonstrated that control measures adopted in selected urban areas had little influence on the ravages of the disease among the population at large and, in 1937, a scheme was launched with the object of controlling malaria on an extensive scale.

Spleen rates by districts — 1939-1955

District	March 1939	March 1940	March 1941	Sept. 1946	March 1947	Sept. 1947	March 1948	Sept. 1948	March 1949	Sept. 1949	March 1950	March 1951	March 1952	March 1953	March 1954	March 1955
Colombo	4.8	3.9	2.9	2.6	2.3	0.8	1.2	1.0	0.7	0.2	0.3	0.25	0.1	0.03	0.05	0.01
Negombo	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1.0	0.0
Kalutara	1.6	0.7	2.2	0.6	0.3	0.3	0.2	0.05	0.01	0.0	0.0	0.0	0.08	0.08	0.2	0.02
Kandy	8.9	7.4	8.6	3.6	2.2	1.6	1.4	1.2	1.1	0.6	0.5	0.29	0.02	0.03	0.02	0.3
Matale	33.0	36.7	24.1	10.4	15.0	12.4	8.9	5.1	2.6	2.3	2.1	2.5	1.0	0.1	0.0	0.0
Nuwara-Eliya	8.4	7.4	10.8	15.2	9.1	1.8	2.2	1.5	2.7	2.5	2.1	1.0	0.5	0.4	0.1	0.3
Galle	4.4	2.5	2.5	2.5	0.5	0.3	0.4	0.01	0.3	0.3	0.3	0.6	0.02	0.1	0.03	0.1
Matara	6.8	16.9	30.7	12.1	9.2	7.3	2.6	0.6	0.5	0.5	0.5	0.7	0.7	0.3	0.4	0.0
Hambantota	58.6	61.3	69.2	52.2	47.4	27.0	30.0	12.4	9.7	3.1	3.05	1.5	1.5	0.2	2.2	1.4
Jaffna	8.5	4.2	4.9	4.3	2.3	2.1	1.1	0.6	1.2	0.3	0.3	0.2	0.03	0.03	0.3	0.2
Vavuniya	66.7	53.9	63.6	65.3	62.2	32.9	23.5	16.0	9.1	4.01	4.0	2.0	0.6	0.0	0.0	0.09
Mannar	43.5	29.7	36.8	22.5	33.7	11.1	12.0	10.3	4.3	0.4	0.5	0.4	0.7	0.4	0.4	0.6
Batticaloa	46.2	29.3	32.5	20.9	16.7	13.1	9.4	6.9	3.8	8.6	1.7	1.5	2.1	1.1	0.7	0.3
Trincomalee	57.7	27.1	23.2	15.9	21.1	21.2	15.2	0.8	11.6	8.6	1.9	1.5	0.0	0.0	0.2	0.0
Kurunegala	34.8	42.1	40.1	33.2	30.8	23.0	15.9	9.4	7.8	5.8	3.7	1.7	1.2	1.2	0.5	0.5
Puttalam	46.0	48.5	38.0	46.1	31.7	24.5	17.5	8.0	4.5	2.6	2.9	2.3	4.2	1.4	0.7	0.0
Chilaw	17.5	18.9	12.4	6.2	6.3	4.7	4.1	4.0	2.4	1.6	2.0	0.08	0.0	0.02	0.04	0.1
Anuradhapura	57.5	70.5	76.6	38.5	36.9	27.1	18.5	12.6	7.1	5.3	3.4	1.9	0.9	0.2	0.2	0.4
Tamankaduwa	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.0	0.0
Badulla	20.2	25.5	28.6	16.3	9.6	8.0	7.8	5.0	4.5	3.4	2.5	4.0	2.5	0.9	0.5	0.3
Ratnapura	11.5	11.1	11.3	7.9	8.7	4.9	2.9	2.3	1.0	0.7	0.25	0.1	0.6	0.1	0.02	0.3
Kegalle	8.1	17.3	11.6	9.9	4.0	4.3	2.9	1.7	1.1	0.9	0.6	0.16	1.08	0.1	0.4	0.3
Ceylon	18.2	17.9	18.4	11.8	10.3	7.6	5.8	3.5	2.7	1.8	1.2	0.8	0.6	0.3	0.3	0.2

Summary of parasite rates by districts for the years 1941-1954

District	March 1941	Sept. 1946	Sept. 1947	March 1948	March 1949	March 1950	March 1951	March 1952	March 1953	March 1954
Colombo	0.6	1.3	0.1	0.04	0.0	0.0	0.0	0.0	0.0	0.0
Negambo	—	—	—	—	—	—	—	—	—	0.0
Kalutara	0.7	0.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Kandy	2.7	2.3	0.3	0.1	0.2	0.04	0.05	0.0	0.0	0.1
Matale	6.8	5.0	0.7	0.5	0.4	0.0	0.2	0.1	0.0	0.4
Nuwara Eliya	1.2	0.9	0.7	0.4	0.2	0.0	0.0	0.0	0.2	0.0
Galle	1.6	0.7	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Matara	11.6	4.3	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Hambantota	14.5	3.6	0.9	0.7	0.2	0.2	0.0	0.0	0.0	0.0
Jaffna	N.S.	0.5	0.4	0.1	0.0	0.05	0.0	0.0	0.05	0.0
Vavuniya	N.S.	0.8	0.0	1.5	0.0	0.0	0.3	0.0	0.0	0.0
Mannar	N.S.	7.8	2.0	1.2	0.3	0.0	0.0	0.0	0.0	0.0
Batticaloa	N.S.	5.1	1.8	2.2	1.0	0.6	1.3	1.6	0.5	0.2
Trincomalee	N.S.	0.3	0.6	1.2	0.0	0.4	0.2	0.0	0.0	0.2
Kurunegala	6.7	10.1	2.6	1.6	0.6	0.6	0.3	0.2	0.2	0.03
Puttalam	2.3	5.0	1.1	1.7	0.0	0.5	0.3	0.0	0.3	1.8
Chilaw	8.6	6.7	0.5	0.6	0.1	0.0	0.0	0.0	0.0	0.0
Anuradhapura	N.S.	3.6	2.7	1.8	0.8	0.1	0.4	0.5	0.5	0.0
Tamankaduwa	—	—	—	—	—	—	—	—	—	0.0
Badulla	3.5	2.2	1.1	0.9	0.6	0.1	0.2	0.2	0.8	0.3
Ratnapura	8.1	4.8	0.9	0.1	0.2	0.0	0.08	0.15	0.0	0.1
Kegalle	0.9	3.3	1.2	0.2	0.1	0.0	0.0	0.0	0.0	0.0
Ceylon	3.7	3.6	0.9	0.6	0.2	0.13	0.16	0.14	0.09	0.07

N. S — Not surveyed.

4. The weekly application of larvicidal oils to streams, which were the main preferential breeding places of the vector species, and ample provision for the treatment of malaria were the main weapons used. Besides hospitals and dispensaries, which undertook this work, all schools and village headmen were used as treatment centers for malaria. All public health personnel, such as sanitary inspectors, public health nurses and midwives, distributed antimalarials to those suffering from malaria, during their routine field visits.

5. In spite of all these intensive efforts made during the period 1937-1946, the disease could not be brought under control.

Infant parasit rates — July 1951 to September 1954 — Summary of results by districts

District	July 51		January 52		September 52		January 53		September 53		January 54		September 54	
	No. exmd.	% pos.	No. exmd.	% pos.	No. exmd.	% pos.	No. exmd.	% pos.	No. exmd.	% pos.	No. exmd.	% pos.	No. exmd.	% pos.
Negombo	163	0.0	103	0.0	146	0.0	193	0.0	253	0.0	298	0.0	459	0.0
Kandy	419	0.0	429	0.0	577	0.0	491	0.0	423	0.2	446	0.0	232	0.0
Matale	120	0.0	122	0.0	233	0.9	230	0.0	157	0.0	194	0.0	233	0.0
Nuwara-Eliya	6	0.0	32	0.0	—	—	18	0.0	64	0.0	36	0.0	50	0.0
Matara	367	0.0	315	0.0	460	0.0	511	0.0	715	0.0	812	0.0	467	0.0
Hambantota	185	0.0	201	0.0	199	0.0	305	0.0	263	0.0	210	0.0	230	1.3
Jaffna	47	0.0	42	0.0	164	0.0	71	0.0	211	0.0	192	0.0	200	0.0
Mannar	109	0.0	78	0.0	91	0.0	97	0.0	136	0.0	107	0.0	88	0.0
Vavuniya	103	0.0	105	0.0	124	0.0	63	0.0	94	0.0	101	0.0	78	0.0
Batticaloa	169	0.0	144	0.0	243	0.0	236	0.4	277	0.4	111	0.0	289	0.3
Trincomalee	13	0.0	10	0.0	88	0.0	49	0.0	103	0.0	92	0.0	58	0.0
Kurunegala	991	0.0	1 064	0.0	1 400	0.1	1 414	0.1	1 061	0.0	922	0.0	841	0.0
Puttalam	67	0.0	29	0.0	44	0.0	29	0.0	67	1.5	78	0.0	89	0.0
Chilaw	415	0.0	475	0.0	428	0.0	442	0.0	440	0.0	459	0.0	430	0.0
Anuradhapura	108	0.0	121	0.0	130	0.0	143	0.0	146	1.4	104	0.9	86	0.0
Tamankaduwa	—	—	—	—	—	—	—	—	—	—	38	0.0	62	0.0
Badulla	91	0.0	79	1.3	106	0.0	106	0.9	134	0.7	128	0.0	218	0.0
Ratnapura	147	0.0	255	0.4	347	0.0	320	0.0	419	0.0	286	0.0	418	0.0
Kegalle	435	0.0	422	0.0	732	0.0	650	0.0	755	0.0	601	0.0	814	0.0
Total	3 955	0.0	4 026	0.05	5 506	0.07	5 368	0.07	5 718	0.1	5 215	0.06	5 342	0.07

III — NATION-WIDE MALARIA CONTROL

1. With the advent of DDT, a nation-wide scheme for the control of malaria by the residual spraying of houses was undertaken and fully implemented in 1947, in which year all malarial areas had been protected by this method. The scheme was a phenomenal success.

IV — MALARIA ERADICATION

1. The subject of malaria eradication in Ceylon was first considered by the Government of Ceylon in 1949. At that time, the concept of malaria eradication was one of attainment by the method of vector eradication. As it was felt that the vector could not be reached in its widespread and also inaccessible sanctuaries in the jungle, the subject was shelved at that time.

2. It was, also, considered at the time that, considering the spectacular reduction of malariometric indices that had occurred during the three years of spraying, a similar decline would continue as the years progressed, and that they would reach zero ultimately.

3. This has been found to be true of the epidemic zone which is a thickly populated opened up area devoid of jungles. Here, malaria transmission has been completely interrupted and, at the same time, the vector has almost completely disappeared. Residual spraying has, also, been interrupted in some of these areas for as long as six years and in all of these for at least three years, up to the present time.

V — INTERRUPTION OF RESIDUAL SPRAYING, 1955

1. Interruption of residual spraying had been done in parts of the epidemic zone as far back as 1952 and had been progressively extended to cover a large part of this zone in later years.

2. In the hyperendemic zone which constituted the greater part of the country, no large scale attempt at interrupting spraying had been done though it had been experimented with by omitting some urban areas from spraying programmes.

3. With the growing tally of anophelines being found resistant to insecticides, and the recommendations being made at the time, therefore, for the early interruption of residual spraying, the few remaining parts of the epidemic zone and the greater part of the hyperendemic zone were omitted from spraying programmes in February, 1955.

4. At the same time, a system of detecting and treating malaria cases was established.

VI — SURVEILLANCE

1. The system of detecting malaria cases was linked with the system of medical facilities existing in the country. There are 256 medical institutions in the area from which residual spraying was now interrupted. Sixty foremen released from spraying duties were trained to take blood smears from all fever cases visiting these institutions, each foreman being assigned four to six institutions each one of which he visited in rotation, working for two weeks at each one and then proceeding to the next, the round of visits being repeated in cycles. These foremen were named vigilance sub-units.

2. Blood smears taken at the medical institutions were despatched to the central laboratory for examination together with a record of names and adresses of those from whom smears were taken.

3. Thirty six public health inspectors also released from spraying duties were termed vigilance units and assigned the task of treating the positive cases detected from the medical institutions. Besides tracing and treating these cases, it was also their duty to investigate these cases and ascertain where infection was acquired and transmission was occurring. These officers when on their routine visits to villages as well as to foci of transmission also took blood smears from all fever cases encountered.

4. Residual spraying and systematic blood smear examination and treatment of cases were undertaken in foci of transmission. All fever cases, including those with past history of fever, were treated as malaria in foci of transmission. Once the initial results of blood smear examinations were obtained, the rest of the cases were treated immediately and a blood smear taken at the same time. All cases were treated with

3 days' treatment with amodiaquine. Five days' primaquine treatment was given to *P. falciparum* cases and 14 days to others.

5. At first the 14 day course of treatment was doled out in five instalments but as treatment became popular, the number of visits for treatment were reduced to three.

VII — CLEARING OF FOCI OF TRANSMISSION

1. Immediate residual spraying was undertaken in foci of transmission. A case survey was then undertaken and all cases treated, inclusive of those with recent history of fever.

After the initial survey, visits were repeated at weekly intervals for two more visits, followed by two visits at fortnightly intervals and then at intervals of a month.

2. Once it was established that there was a focus, blood smear examination was done as a routine, but treatment was undertaken irrespective of the results. Persons with past history of fever were treated but no efforts were made to treat all persons or even other inmates of houses with malaria. In all instances not established to be as *P. falciparum* infection, the 14 day course of primaquine was given.

3. It has been found that by this method villages where a large number of cases had occurred could be cleared completely, and have remained free of transmission, thereafter.

VIII — PROGRESS OF THE MALARIA ERADICATION PROGRAMME

1. When spraying was interrupted in February, 1955, and surveillance organised, it was found that there were 514 positives detected during this month among 9,585 smears examined, the percentage positive being 5.9 %. During the previous month, there had been 16 % of positives among 1,450 smears examined. These smears, however, were not comparable with those obtained in the surveillance programme where blood smears were from all fever cases. The 1,450 smears were sent from medical institutions from cases suspected to be malaria.

2. At the commencement of the work, therefore, there were no data or blood smear examinations, which could be taken as base-line

Results of examination of blood smears 1955-1958 (July)

	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total for year
					1955								
Number Examined	1 450	9 585	9 474	6 396	9 070	8 956	9 983	10 591	8 456	9 777	9 325	10 662	103 725
Number Positive	244	514	342	165	182	235	182	195	215	440	472	612	3 795
Percentage Positive	16.1	5.9	3.6	2.5	2.0	2.6	1.8	1.8	2.5	2.9	5.06	5.7	3.7
					1956								
Number Examined	10 389	10.442	9 263	6 961	10 901	14 415	11 471	1 099	10 263	11 557	11 705	12 814	121 280
Number Positive	374	277	446	164	311	264	557	510	792	568	908	1 822	6 994
Percentage Positive	3.6	2.6	4.8	2.4	2.9	1.8	4.9	5.04	7.7	4.9	7.8	14.2	5.8
					1957								
Number Examined	13 727	10 365	10 912	6 437	7 110	7 744	8 842	9 436	7 458	7 297	10 718	5 911	105 957
Number Positive	2 407	1 132	706	386	392	433	443	284	166	173	163	126	6 811
Percentage Positive	17.5	10.9	6.5	6.0	5.5	5.6	5.01	3.0	2.2	2.4	1.5	2.1	6.4
					1958								
Number Examined	5 598	4 872	6 182	3 532	4 065	3 130	4 862	—	—	—	—	—	—
Number Positive	208	105	91	22	43	19	36	—	—	—	—	—	—
Percentage Positive	3.7	2.25	1.5	.6	1.1	.6	.7	—	—	—	—	—	—

data, and the first year's data now being obtained had to serve as such, as well as to serve the purpose of evaluation of the work being done.

3. During the first two months of surveillance, several large foci of transmission were detected and cleared and these have remained clear up to the present time. These two months were also the tail end of the transmission season in the hyperendemic zone. From then on, until August, 1955, the number of cases showed a decline until the beginning of the next transmission season in October, 1955.

4. This season October, 1955 to March, 1956 ended with no definite indication that in spite of over an year's interruption of spraying there had been any deterioration in the position from February, 1955.

5. The investigation of cases detected, indicated that transmission was at a standstill in the epidemic zone even as it is now. Quartan malaria had practically disappeared from all parts of the country. *Vivax* and *falciparum* infections had, however, persisted in numbers. The reason was that, what may be termed a subsidiary epidemiological cycle of transmission had continued in the hyperendemic zone, untouched by the residual spraying programme.

6. During the rainy season, which was also the transmission season in the hyperendemic zone, the inhabitants of these parts were in the habit of taking up temporary residence and growing their food in jungle clearings far removed from their permanent abodes in villages. The jungles being the property of the Government, the clearings were kept secret and these sites were changed from year to year. The vector species being abundant in the streams along which such cultivation took place, malaria transmission took place.

7. This activity of jungle clearing and food cultivation which took place from September to March had maintained a fairly large parasite reservoir among a population that for the balance of the year lived in sprayed houses where no transmission took place.

8. Eighteen months after the interruption of spraying in July, 1956, the picture started to change rapidly. There were 557 cases detected during this month against a 182 during the corresponding month of the previous year, the percentage positive being 4.9 % compared to 1.8 %. The next month, August, was similar to the previous month. Transmission was confined to a particular province where the seasonal rise was ahead of the usual rise occurring in other parts of the hyperendemic zone.

9. With the commencement of the seasonal rise at the end of the year, it was seen that the increasing transmission was generalised throughout the hyperendemic zone. What is more, it was seen that while earlier transmission was confined to jungle clearings, the transmission now occurring also affected, on a large scale, permanent villages in which spraying had been interrupted for eighteen months.

10. Entomological surveys that had been carried out since the interruption of spraying indicated that the vector species, that had disappeared from villages that had been sprayed, had now re-appeared in them after interruption. The return of the vector was from the jungles along the streams that traversed both jungles and permanent villages.

11. The epidemic zone which is thickly populated and devoid of jungle was not affected by this resumption of transmission. Here, progressive interruption of spraying had been commenced since 1952, and malaria which was unstable in this area had been eradicated.

12. There were, also, two districts in the hyperendemic zone that were not affected by the resumption of transmission. They were Hambantota and Ratnapura districts. After six months of surveillance in 1955, it was found that a large number of cases were being detected at medical institutions in the area and that foci of transmission were widespread. Residual spraying was, therefore, resumed in these districts, while at the same time more officers were employed in detecting cases. Instead of one officer being assigned four institutions for work during a cycle of visits lasting eight weeks, an officer was assigned two institutions, only, which he worked on alternate fortnights. In these two districts, cases have now been reduced to negligible numbers.

13. With the resumption of generalised transmission in the hyperendemic zone, residual spraying was also resumed. The number of cases occurring were too many for systematic surveillance. All medical institutions were, therefore, supplied with 4-amino-quinolines and 8-amino--quinolines with instructions for their proper use. The surveillance organisation as existed did their best under the prevailing conditions and visits for treatment were temporarily curtailed to one visit, only. The number of positives recorded for the period September 1956 to March 1957, are only as many as could have been obtained with the existing organisation that was inadequate for that particular period. The rapid decline in cases from this period onwards speaks for the efficacy of the measures adopted.

IX — READJUSTMENT OF THE ERADICATION SCHEME

1. With the resumption of transmission occurring in the hyperendemic zone, plans were drawn up for the readjustment of the eradication scheme. In this readjustment, it was proposed that the spraying be resumed in the hyperendemic zone and this was done by the end of 1956.

2. The plans for the intensification of surveillance have, however, been held up due to the absence of additional laboratory accommodation required. This difficulty is, however, being overcome.

3. The surveillance system to be adopted has been tried out and found to be successful in the two districts mentioned earlier. In Ceylon, there are dispensaries for treatment of the sick, generally at a distance of ten miles from one another. Further, visits are made from each of these dispensaries to intermediate stations one or more times each week.

4. It is, therefore, proposed to station a full-time officer at each of the 256 dispensaries in the hyperendemic zone. This officer will, also, work at the intermediate stations served by each dispensary. Blood smears will be taken from all fever cases visiting these institutions.

5. The investigation of positives detected at these dispensaries and their treatment, as well as field surveys will be undertaken by the thirty six vigilance units already in existence, and who will now be all supplied with jeeps. After an initial period at dispensaries, and when dispensaries cease to be fruitful for cases, the officers working at dispensaries will be banded together under the vigilance units to form teams for part of their time and will undertake mass surveys in the field, taking smears from all persons visited.

6. Regional supervisors and vigilance officers who now have three to four year's experience of their areas are now adept at ascertaining the whereabouts of jungle clearings. These field surveys will commence in these clearings which are inhabited during the transmission season. Villages to which the people return after the cultivation season will be taken up next.

7. Interruption of spraying will be undertaken on the basis of the findings of these surveys.

Malaria cases by districts — 1955-1958

Name of district	1955		1956		1957		1958 (up to July)	
	No. exmd.	No. pos.	No. exmd.	No. pos.	No. exmd.	No. pos.	No. exmd.	No. pos.
Colombo	362	14	224	17	487	14	316	3
Negombo	424	2	335	6	575	6	145	0
Kalutara	10	4	5	1	5	3	0	0
Kandy	2 587	154	5 491	136	5 314	121	1 708	44
Matale	8 691	305	9 935	820	6 333	782	1 587	78
Nuwaraeliya	2 593	13	1 467	151	1 247	7	555	2
Galle	2	0	27	1	4	0	0	0
Matara	1 064	46	922	7	884	7	521	0
Hambantota	7 702	599	11 102	301	6 260	22	2 332	30
Jaffna	6 659	150	5 075	129	5 324	284	2 055	30
Mannar	3 539	55	7 403	81	5 591	367	1 096	7
Vavuniya	3 867	133	7 148	232	5 774	312	1 783	67
Batticaloa	11 347	860	17 807	1 566	13 899	736	6 284	60
Trincomalee	2 420	18	1 673	89	2 597	114	711	11
Kurunegala	17 093	178	15 306	1 309	9 845	1 876	2 587	99
Puttalam	3 592	52	1 993	13	1 786	51	826	10
Chilaw	2 997	7	3 252	18	2 760	38	895	0
Anuradhapura	14 095	180	16 726	638	11 838	1 057	1 457	53
Tamankaduwa	3 617	389	5 785	643	3 000	348	272	5
Badulla	6 311	317	9 552	909	11 649	640	3 026	20
Ratnapura	6 629	392	7 712	61	8 578	12	3 134	4
Kegalle	2 204	6	1 132	11	2 207	14	951	1

X — SUMMARY AND CONCLUSIONS

1. After several years of residual spraying of houses, Ceylon had been converted into a uniformly «healthy» country, as judged by standards set for malaria control, and residual spraying was then interrupted.

2. In the thickly populated epidemic zone devoid of jungle sanctuaries of the vector species and where virtual eradication of the vector had been attained, three to six years of interruption of spraying has resulted in no resumption of transmission.

3. Interruption of spraying in the hyperendemic zone, however, resulted in the generalised resumption of transmission in this zone, after a period of eighteen months of interruption. The reservoir of infection present in this zone was the result of a subsidiary cycle of transmission which had been taking place because of certain features associated with the habits of both man and vector species.

4. Malariometric surveys and standards set for malaria control do not appear adequate under all situations as an indication for interruption of residual spraying. Epidemiological investigations and surveys to ascertain the level of any remaining reservoir of infection appear indispensable, before interruption of spraying is done. The permissible level of infection, if any is to be permitted, must however vary within wide limits from vector to vector and from country to country and, even in respect of the same vector, in the same country in different environments.

5. In Ceylon, distances being short, populations concentrated and medical facilities being what they are, it has been found that the method of using a medical institution to obtain a pointer to a focus of transmission, and then tracing a case to its origin is a satisfactory method of detecting and clearing residual foci of transmission and eliminating the reservoir of infection.

The organisation for this purpose has, however, to be strengthened.

6. Large scale parasite surveys, in the field, of all persons, with particular attention to potentially dangerous groups but including others as well, will be carried out before interruption of spraying. The frequency of repeating these surveys will be determined on the basis of the results of initial surveys.

7. After ten years of residual spraying alone, there were 5.9 % positives for malaria parasites among all fever cases examined in February, 1955. In January, 1957, at the peak period of resumption of transmission, there were 17.5 % positives. This percentage has rapidly declined to 0.6 % and 0.7 % in June and July, 1958.

8. On the face of an inadequate organisation for surveillance such rates which had not been reached by ten years of spraying, alone, have now been achieved by harnassing the medical institutions for treatment with modern anti-malarials, while the spraying programme was resumed.

9. Seasonal variation in a malaria morbidity curve, however small its amplitude, should be viewed with concern in a malaria eradication programme. If the methods being adopted for eradication are achieving success, the curve should continue in an uninterrupted downward trend. Any flattening of the curve may indicate a problem unknown and yet to be solved before the attainment of eradication, or possibly the limit attainable with the available resources

10. Malaria presents a dynamic problem and we may plan so far, but, perhaps, no further; yet we should maintain ourselves sufficiently wide-eyed and elastic, to contend with any changing situation that might be for or against us.

GENERAL DISCUSSION

Dr. Luís Vargas (México) — In several papers presented mention is made to behaviouristic resistance to insecticide. But values that might permit comparison are lacking.

Busvine and Nash, and Fay, working independently have laid the foundations for a useful methods to measure the physiological resistance to insecticides used in the Malaria Eradication Programms. Perhaps it is convenient at this moment to invite contributions aiming at the proposal of a method of universal use that uniformly could measure the reactions of the anophelines to avoid total or partial contact with insecticides.

Dr. C. Alvarado (Argentina) — Venezuela is one of the leading countries on malaria eradication in the Americas and all over the World. We must congratulate Dr. Gabaldon and his co-workers for their paper and achievement.

Dr. Gabaldon comenting the causes of residual foci gave a good example of the consequence of incomplete spray when said that residual foci are due mostly to delayed spraing cycles or to houses left without spraying, giving the 49.1 per cent of the indigenous cases found in the last three years.

I consider very important to call the attention to this fact that occurred in a malaria service of so high operational standard, as a remind to every eradicator, that *operational deficiencies* are of primary importance in malaria eradication.

I want ask Dr. Gabaldon about the level of susceptibility of the vectors in areas of refractory malaria and in other areas where malaria transmission is still been transmitted.

(Dr. Manuel T. V. de Meira)

Dr. Fernando M. Bustamante (Brazil) — Dr. Meira refers to the possibility of using chloroquinized salt for malaria eradication in an island of the archipelago of Cabo Verde. As I was informed by himself a few days age there are in such island very favourable conditions for using drugs in salt for all the salt comes from outside the island, there are large amounts of salt used for animals or other purposes, the climate is dry and there are all the facilities to treat salt with drugs.

However, I understood by his paper that eradication of *A. gambiae* in Cabo Verde seems to be feasible by D. D. T. house spraying. So, I ask to Dr. Meira to inform wether the island suggested to be protected by salt with cloroquine is the same when he thinks to be feasible the eradication of *A. gambiae* by residual insecticides.

(Dr. Arnoldo Gabaldon)

Dr. Gabaldon says in his paper that malaria was or will be eradicated from Venezuela in areas with transmission by *A. darlingi* by means of residual insecticides.

I ask to Dr. Gabaldon wether this is true even for the Amazon region of Venezuela.

(Gabaldon, Meira, Roque)

Dr. E. PAMPANA (Italy) — Emphasizes the significance of Gabaldon's findings of *falciparum* infections in Venezuela: out of 39 localities in which were reported, 38 were within 50 km of the border — This shows the importance of international protection.

Meira's report shows interruption of transmission in an African island, situated in tropical areas, with *gambiae* as a vector and a high percentage of *vivax* infections, but one wonders whether the same result could have been had if the area were not an island and if the D. D. T. had not grafted itself on a post-epidemic decline of morbidity.

Expressed his interest in Roque's findings which confirm Raffaele & Coluzzi's reports on the individual testing of mosquitos, in insecticide-susceptibility tests, as opposed to the simultaneous testing of various specimens in a single tube. He will report these findings to the entomologists of WHO in Geneva.

Dr. RAUL D'ALMEIDA ROQUE (Portugal) — Je demande au Docteur Gabaldon qu'il ait la bonté de nous renseigner sur l'origine des cas importés de l'étranger.

Dr. M. MEIRA (Portugal) — Je répondrai à Mr. Bustamante.

L'île en question est celle de Santiago, où je pense qu'il sera trés intéressant de faire une application de la méthode du Docteur Pinotti, avec du sel cloroquiné. Il y a surtout des raisons d'ordre économique, à ce moment, pour préferer l'usage de cette méthode à celle des insecticides, dont l'aplication on limitera d'ailleurs à une petite zone, de cette même île où il existe de la filariose bancroftienne.

Dr. A. Gabaldon (Venezuela) — In reference to susceptibility of vectors in refractory areas in data presented last month by Dr. J. Blasquez, in charge of the toxicology laboratory of the Malaria Division, did not show any signs of resistance. As stated in the paper we have found impossible in practice to spray all houses of a locality, and even whole localities are delayed in receiving their spraying on time, particularly during the rainy season, when communications become very difficult. These delays have special influence in areas where imported cases arrive frequently. In the Amazonia Region of Venezuela we may have a problem of out door transmission due to *A. darlingi,* which is here also zoophilic.

The practice of epidemiological surveillance in this area is particularly difficult because of language and cultural problems with Amerindian tribes inhabiting this territory. The data collected so far have not allowed us to make definite conclusions in this respect. In reference to the origin of imported cases I may say that they do not come only from areas of the neighbouring countries, but that cases originating in some European, African and Asiatic regions have also been found.

Sir GORDON COVELL (U. K.) — I wish to draw attention to a campaign in India which has not received the recognition it deserves and which was one of the first in which D. D. T. was used in a large scale. In 1945 I was able to secure 2 tons of D. D. T. for use in the Kanara District of Bombay State when the local antimalaria service was under the direction of Dr. D. K. Viswanathan. The results have been extremely striking and seven years ago 16 million persons were under protection by residual insecticides at very low annual cost. I believe that at the present time 30 million persons are under such protection and whole tracts of land previously untilled are now under cultivation. In my opinion this campaign conducted with such brilliant success and protecting a population nearly seven times as great as that of Venezuela, is one of the most outstanding which has yet been accomplished.

Dr. GEORGE GIGLIOLI (U. K.) — I have listened with much interest to all the papers submitted in this Section and I wish to congratulate the Authors.

The paper of Drs. Gabaldon and Gunarathna offer a very valuable lesson in respect to the very important point concerning the training of malariologists and malarial entomologists; as Prof. Pampana has told us this constitutes a very important phase of WHO activities.

Venezuela, for over 20 years, has had one of the most efficient, best endowed and most brilliantly led malaria services: yet we have heard this morning that in the 12th year of this eradication campaign, three quite distinct residual epidemiological and eradication problems still await solution. It is only when an eradication campaign has reached its more advanced stages that such unpredictable problems are likely to make their apparence and it is at this stage that the preparation of the malariologist will be put to the hardest test.

3RD SESSION: *Saturday, September 13th, 9:00 to 10:30 a.m. Room D*

The meeting was held under the Chairmanship of Dr. Arnoldo Gabaldon and Dr. H. T. Soeparmo.

The Rapporteur was Dr. Fernando Bustamante and the Secretary was Dr. Manuel T. V. de Meira.

The following papers were presented and discussed:

CONSIDERAÇÕES SOBRE CERTOS PROBLEMAS ESPECIAIS RELACIONADOS COM A ERRADICAÇÃO DA MALÁRIA NO BRASIL

F. M. BUSTAMANTE[1]

No Brasil não são conhecidos anofelinos vectores essencialmente exófilos, de que é exemplo o *A. bellator* em Trinidad, B. W. I., e nem essencialmente endófilos, como o é o *A. darlingi* na baixada costeira da Guiana Inglesa e na parte central da Venezuela.

Todas as espécies vectoras importantes conhecidas no País (*A. darlingi, A. aquasalis, A. albitarsis, A. cruzii cruzii* e *A. bellator*) podem ser esquemàticamente consideradas como nem essencialmente endófilas, nem essencialmente exófilas. Ademais, apresentam elas sensíveis variações regionais de comportamento, quer no que toca à sua endofilia-exofilia (todas as espécies), quer no que se refere à sua capacidade vectora, as três últimas espécies sendo vectoras em algumas áreas e sem importância epidemiológica em outras, ao passo que as duas primeiras são vectoras em toda a sua área de distribuição.

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[1] Chefe executivo da Campanha de Erradicação de Malária, Departamento Nacional de Endemias Rurais, Ministério da Saúde, Rio de Janeiro, Brasil.

O grau de domesticidade ou endofilia do *A. aquasalis* não é o mesmo, ao longo da nossa extensa costa, sendo muito maior nos Estados do Nordeste, centro da sua área de distribuição no País, que mais para o norte, ou mais para o sul, onde o número de exemplares colhidos em capturas ao relento com isca animal é muito elevado. Mas, apesar desses factos, o *contrôle* da malária transmitida por esta espécie com aplicações domiciliares de D. D. T. foi, de modo geral, excelente, sendo mesmo completamente eliminada a sua transmissão em certas zonas.

Dados de certas áreas do Nordeste indicam que, nessa região, onde é mais acentuada a endofilia da espécie, diminuiu muito a densidade do *A. aquasalis,* por factores ainda não completamente esclarecidos, sendo provável que o emprego do D. D. T. no interior das casas seja um desses factores.

O facto inconteste é que, apesar de bastante exófilo em certas áreas, não se conhecem problemas de malária refractária aos insecticidas na área de transmissão por *A. aquasalis.* A possibilidade da transmissão extradomiciliar por essa espécie foi demonstrada pelo encontro de exemplares infectados com esporozoitos, colhidos em capturas ao relento, em Belém, Pará (Galvão, Damasceno e Marques, 1942). Mas, por outro lado, a espécie é de baixa tendência antropófila, nessa área, segundo observações, com provas de precipitina (Deane, Vernin e Damasceno, 1949). Assim, com a eliminação da transmissão intradomiciliária pelo insecticida residual, as possibilidades de transmissão extradomiciliária pelo *A. aquasalis* ficariam muito reduzidas, parecendo não apresentar esta espécie qualquer problema especial, mesmo nas áreas em que é mais exófila que endófila.

O *A. albitarsis* é a espécie vectora de mais larga distribuição geográfica, sendo encontrada em todo o País. É um mosquito zoófilo na maior parte da sua área de distribuição, possuindo certo grau de endofilia sòmente em determinadas partes do litoral, onde é um transmissor geralmente associado ao *A. aquasalis* ou ao *A. darlingi,* ou a ambos.

Aparentemente, o emprego do D. D. T. no interior das casas não afecta a densidade geral do *A. albitarsis*; mas a sua baixa capacidade vectora, mesmo nos trechos do litoral em que se apresenta com maior endofilia, é de molde a facilitar a erradicação da malária por ela transmitida, com insecticidas residuais. Na realidade, o *contrôle* da malária com D. D. T. foi excelente nos trechos do litoral do Brasil em que o *A. albitarsis* é vector comprovado.

O *A. darlingi,* o *A. cruzii cruzii* e o *A. bellator* são espécies de características muito diversas das acima referidas, com relação ao seu comportamento frente aos insecticidas residuais.

Conforme já assinalámos (Bustamante, 1951), o *A. darlingi* é bastante exófilo na região central do Brasil, provável centro de dispersão desta espécie na América do Sul (Gabaldon, 1953), diminuindo a sua exofilia para leste e para o sul.

Na extensa área de distribuição do *A. darlingi,* a eficácia dos insecticidas clorados na erradicação da malária relaciona-se com o comportamento biológico da espécie e, em certas regiões, com o tipo de habitação.

Os factores relacionados com os hábitos do *A. darlingi* e que podem constituir problemas locais ou regionais a dificultar a erradicação da malária no Brasil, com insecticidas de acção residual, são, em resumo, os seguintes:

1. O grande número de mosquitos que se alimentam no homem fora das habitações, no peridomicílio ou em pleno campo, nos grandes vales do planalto central e na região amazónica, onde, conforme observações anteriores (Bustamante, 1951), confirmadas por outras mais recentes, a densidade da espécie continua elevada, apesar das aplicações domiciliares de D. D. T.;

2. A possibilidade de transmissão extradomiciliária de malária nessas condições. Testes de precipitina levados a efeito em Belém, na região amazónica (Deane, Vernin e Damasceno, 1949), indicam acentuada antropofilia do *A. darlingi* e Deane (1957) encontrou infectado com esporozoitos um exemplar de *A. darlingi* capturado com isca animal ao relento, nos arredores de Porto Velho, território federal de Rondónia;

3. A possibilidade de transmissão intradomiciliar por mosquitos que se retiram para abrigos extradomiciliários, seja como consequência de modificação de comportamento adquirida pela espécie, seja em virtude da existência de raça normal, caracterizada pelo hábito de alimentar-se dentro de casa e abrigar-se no exterior (Gabaldon, 1953). Esta possibilidade foi por nós admitida na área de Engenheiro Dolabela, vale do rio Jequitai, afluente do rio São Francisco, no Estado de Minas Gerais (Bustamante, 1957). Nessa área fazíamos duas e, posteriormente, três

aplicações domiciliárias de D .D. T. em todas as casas, sem que conseguíssemos eliminar completamente a transmissão da plasmodiose. A maioria dos casos de malária registados poderia ser explicada por transmissão extradomiciliar por *A. darlingi*, não encontrado dentro das casas dedetizadas, mas colhido em grande número nas paredes exteriores de algumas delas (Bustamante e col., 1951) e em capturas ao relento com isca animal ou humana. Mas certo número de casos de malária registados em lactentes levou-nos a admitir que, pelo menos, uma parte da transmissão residual verificada ocorria dentro das casas dedetizadas. Por outro lado, outras observações realizadas na mesma área (Bustamante e col., 1952) revelaram que a grande maioria dos exemplares de *A. darlingi* que penetrava em casa recentemente borrifada com D. D. T. dela se retirava ràpidamente, antes ou depois de sugar os moradores, certo número deles podendo sobreviver.

Antes de iniciado o emprego do D. D. T. nessa área, o *A. darlingi* era capturado em altos números, em repouso nas habitações, durante o dia.

De 1946 a 1955, quando o D. D. T. foi regularmente empregado de 6 em 6 meses e, posteriormente, de 4 em 4 meses, foram muito raros os exemplares de *A. darlingi* encontrados dentro das casas, em capturas diurnas. Em 1956 o insecticida foi suspenso na área (última aplicação em Abril), onde se passou a empregar o sal cloroquinado; mas as capturas diurnas não revelaram a presença do vector nas casas senão cerca de 2 anos após a última aplicação de D. D. T. e, mesmo assim, em números bastante reduzidos, como revelam os seguintes dados:

Março de 1946: 520 *A. darlingi* em 178 casas inspeccionadas (cerca de 3 mosquitos por casa);

De 1947 a 1955: raríssimos os exemplares encontrados durante o dia dentro de casas dedetizadas;

Março de 1958: 4 mosquitos em 449 casas;
Abril de 1958: 43 mosquitos em 317 casas;
Maio de 1958: 13 mosquitos em 805 casas.

É de se notar que essa baixa densidade do *A. darlingi* dentro das casas não se deve à redução da densidade geral da espécie, que continua muito elevada nessa área, mais de 4 mil mosquitos tendo sido colhidos em capturas ao relento com isca animal, de Março a Julho do ano corrente (cerca de 70 mosquitos por hora de captura).

A ocorrência de situações epidemiológicas como a estudada na área de Engenheiro Dolabela poderá ser observada apenas em zonas do planalto central e do vale amazónico, em que condições ecológicas excepcionalmente favoráveis propiciam uma densidade muito elevada da espécie. Nossas observações mostram que na periferia da área de distribuição do *A. darlingi*, onde a espécie é mais endófila (Baixada Fluminense e em outros trechos do litoral), bem como nos vales do planalto central com malária instável (áreas dos Estados do Paraná, Minas Gerais, Goiás e São Paulo, compreendidas na bacia do Paraná) e em outros vales malarígenos com idênticas características epidemiológicas (vales do Acaraú e do Poti, Estado do Ceará), onde as condições ecológicas habituais não permitem uma elevada densidade do vector, o emprego do D. D. T. em aplicações intradomiciliárias produziu excelente *contrôle* da malária, acompanhada de acentuada redução ou aparente eliminação da espécie vectora.

Por outro lado, em certos vales do Planalto Central e da bacia amazónica, os resultados da aplicação domiciliar de D. D. T. no programa de *contrôle* são de modo geral menos favoráveis. Aí, onde a densidade do *A. darlingi* for excepcionalmente elevada, embora o grosso da transmissão seja eliminado pelos insecticidas, a grande actividade extradomiciliar do vector, a sua acentuada antropofilia e outros factores biológicos já referidos poderão criar dificuldades à erradicação da doença.

Acreditamos que, excluída a região amazónica, na maior parte da área de transmissão por *A. darlingi* a malária poderá ser erradicada com insecticidas. Dentro dessa área deverão ficar, todavia, focos de extensão variável, com transmissão residual consequente a um ou mais dos factores acima referidos, relacionados com a biologia do transmissor.

Outro problema especial na área de transmissão por *A. darlingi* é a existência de certo número de habitações rudimentares, desprovidas total ou parcialmente de paredes, em zonas de garimpos, de seringais e outras. Tais habitações não podem ser convenientemente protegidas pelos insecticidas e, ainda que não sejam muito numerosas, podem constituir sério problema, especialmente quando disseminadas em área muito extensa, como a região amazónica. De 70 769 casas recenseadas no Estado do Amazonas, 3 918 (5,5 %) são palhoças desprovidas de paredes, havendo ainda 9 636 (13,6 %) de palhoças primitivas, muitas parcialmente sem paredes.

Nessa mesma área merece ser referido o nomadismo de certos grupos, como garimpeiros, seringueiros e lenhadores, que constroem habitações provisórias próximas do local em que estão trabalhando, mudando-se depois para novas habitações em outro local; e os habitantes de certas pequenas cidades e vilas, que se transferem para habitações provisórias na zona rural, por ocasião das plantações e das colheitas.

O *A. cruzii cruzii* e o *A. bellator*, únicos responsáveis pela transmissão da malária no litoral Sul do Brasil [1], desde o Município de Cananeia (Estado de São Paulo), até o Município de Torres (Estado do Rio Grande do Sul), em uma área que compreende cerca de 44 000 quilómetros quadrados, apresentam também hábitos peculiares capazes de dificultar a erradicação da malária com insecticidas.

Os seguintes factos relacionados com a biologia desses vectores eram conhecidos antes de iniciadas as aplicações de D. D. T. nas casas (Pinotti, Rachou e Ferreira, 1947; Coutinho, Rachou e Ricciardi, 1943; Rachou, 1946; Rachou, 1946-*a*):

1. Ambos frequentam em altos números os domicílios, onde podem ser capturados sugando os habitantes ou repousando nas paredes ou tectos;
2. O número de exemplares encontrados dentro das casas é muito maior em capturas nocturnas do que em capturas matinais ou diurnas;
3. Durante capturas nocturnas e diurnas observavam-se, algumas vezes, mosquitos evadirem-se das casas, logo após o repasto sanguíneo;
4. Podem ser capturados em grande número com isca humana ou animal, a qualquer hora do dia ou da noite, perto dos criadouros e nos arredores das casas à noite. Certa preferência pela isca humana em capturas extradomiciliárias sugere que as duas espécies são mais antropófilas do que zoófilas, mesmo quando no exterior das casas;
5. Em certas localidades têm sido encontrados à noite repousando nas paredes externas das casas;

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[1] Além dessas espécies, o *A. homunculus* é provável vector em certa área do Est. de S.ta Catarina (Rachou e Ricciardi, 1943).

6. Exemplares naturalmente infectados com esporozoitos foram encontrados em várias oportunidades, colhidos, quer no interior quer no exterior das habitações, com isca humana ou animal.

A partir de 1949 o *contrôle* da malária na região passou a ser feito com aplicações domiciliárias de D. D. T., uma vez por ano, obtendo-se grande redução na incidência da doença. Entretanto, os resultados foram muito menos favoráveis em certos pontos do que em outros da mesma área e de modo geral inferiores aos obtidos com o D. D. T. em área de transmissão por outras espécies. Embora se tratando de um programa de *contrôle* em que não havia cobertura integral com o insecticida, certos factos sugeriam fortemente que na área de transmissão por *A. cruzii cruzii* e *A. bellator* a malária poderia ser parcialmente refrectária ao D. D. T. Em primeiro lugar, a transmissão pràticamente desapareceu ou foi muito mais reduzida em certas zonas, permanecendo mais intensa em outras em que o insecticida era aplicado da mesma maneira. Em segundo lugar, em uma pequena localidade (Guaporanga, Estado de Santa Catarina), em que eram muito frequentes os casos de malária, o insecticida foi empregado de maneira muito satisfatória, com intervalos de 6 meses, a partir de Abril de 1955, sem que a situação se modificasse.

Em 1954, foram encontrados nessa localidade dois exemplares de *A. cruzii cruzii* infectados com esporozoitos: 1 colhido em abrigo natural (146 dissecados) e 1 colhido no interior de uma casa, à noite (112 dissecados).

Procurando confirmar as nossas suspeitas, realizámos, em uma outra área do Estado de Santa Catarina onde os casos de malária eram bastante frequentes, apesar do programa de *contrôle,* aplicações de pó molhável de D. D. T., em todas as casas, com intervalos de 4 meses. Nessa observação o insecticida foi empregado sem falhas, com supervisão rigorosa, em Fevereiro, Junho e Outubro de 1955 e em Fevereiro e Junho de 1958 e os resultados não deixam dúvidas, pois certa transmissão residual continua presente. Trata-se de pequena área com 54 casas e cerca de 250 habitantes, em que ocorreram 46 casos de malária em 1957 e 14 casos de Janeiro a Junho de 1958, a maioria deles sendo infecções autóctones.

Ferreira e Azambuja (1955) registaram o encontro do *A. cruzii cruzii* e do *A. bellator* nas paredes exteriores de casas dedetizadas em densidade três vezes maior do que no interior das mesmas casas e admitem que esse achado poderia significar uma modificação de comportamento, determinada pelo insecticida. É difícil a confirmação dessa hipótese, mas, aparentemente, o insecticida pode ter exacerbado a tendência natural dessas espécies de sugar no peridomicílio e de permanecer pouco tempo dentro das casas.

Como no caso do *A. darlingi,* acreditamos que os insecticidas de acção residual, aplicados de modo integral, do ponto de vista qualitativo e quantitativo, deverão erradicar a malária de grandes partes da área de transmissão por *A. cruzii cruzii* e *A. bellator* onde a densidade dessas espécies não seja muito elevada. Entretanto, deverão permanecer focos residuais, mais ou menos extensos, em núcleos demográficos localizados muito próximos a florestas altamente infestadas por bromeliáceas, onde predomina o *A. cruzii cruzii.*

De um modo geral, pode dizer-se que o *contrôle* da malária com D. D. T. foi muito melhor nas zonas em que, por motivos naturais ou pelo maior desenvolvimento agrícola, era mais baixa a densidade de bromeliáceas e, consequentemente, das espécies acima referidas.

Testes de susceptibilidade com a técnica de Busvine Nash realizados em alguns pontos do País, com *A. darlingi, A. cruzii cruzii* e *A. aquasalis,* revelaram susceptibilidade normal destas espécies ao D. D. T. (Rachou e col., 1957, 1957-*a* e 1958).

Investigações realizadas por Paulini (1956) revelaram alto poder desactivante do D. D. T. por amostras de barro colhidas em vários pontos do País. Segundo o mesmo autor (Paulini, 1958), cerca de 50 % das amostras de barro por ele examinadas tiveram poder absorvente desprezível, cerca de 25 % mostraram baixa adsorção e sòmente 25 % adsorviam o insecticida ràpidamente. Ainda não temos dados seguros para julgar a importância prática desse fenómeno, mas em várias localidades cujo barro mostrou elevado poder adsorvente o *contrôle* da malária com D. D. T. foi muito satisfatório.

Dessa maneira, podemos dizer, em resumo, que as observações até agora realizadas no Brasil sobre o comportamento das espécies vectoras e sobre os resultados do *contrôle* da malária por elas transmitida, nos convencem de que não haverá dificuldades para erradicação da malária com insecticidas nas áreas de transmissão por *A. aquasalis* e por *A. albitarsis,* sendo de prever-se, entretanto, certos problemas especiais nas áreas com transmissão por *A. darlingi,* por *A. cruzii cruzii* e por *A. bellator.*

POSSÍVEIS SOLUÇÕES PARA OS PROBLEMAS ESPECIAIS

Focos de malária parcialmente refractária aos insecticidas na área de transmissão por *A. darlingi*, *A. cruzii cruzii* e *A. bellator* poderão ser eliminados por meio de drogas. A extensão da área, a sua população e outros factores determinarão a escolha do medicamento e a maneira mais eficiente e mais económica de empregá-lo, se pelo método clássico de distribuição periódica de comprimidos, de casa em casa, ou se de mistura com o sal de cozinha (método Pinotti). Em outra comunicação (Bustamante, 1958), apresentamos alguns recentes resultados obtidos no Brasil com este método. Por outro lado, os resultados de observações que estamos a realizar no Estado de Santa Catarina com o Dr. Mário Ferreira sugerem que 0,025 g de pirimetamina de trinta em trinta dias podem ser suficientes para suprimir a transmissão por *A. cruzii cruzii*, em áreas pequenas.

O uso adequado de certos medicamentos, entre os quais a pirimetamina e a primaquina, desde o início ou nos dois últimos anos da fase de cobertura integral com insecticidas, poderá mesmo prevenir o aparecimento de focos residuais de transmissão, se aplicados com oportunidade nas zonas em que estes são suspeitados, embora tal procedimento eleve o custo do programa.

Para eliminar focos residuais de malária transmitida por *A. cruzii cruzii* e *A. bellator* dispomos ainda dos recursos mecânicos ou químicos de destruição das bromeliáceas, tais como o seu arrancamento manual e o desmatamento ou o emprego de bromelicidas. Qualquer desses recursos capazes de baixar sensìvelmente a densidade dos vectores contribuirá de maneira decisiva para a eliminação de eventuais focos de malária refractária aos insecticidas, na área de transmissão por *A. cruzii cruzii* e *A. bellator*.

O GRANDE PROBLEMA DA REGIÃO AMAZÓNICA

Como já referimos anteriormente, a região amazónica constitui o maior problema com que se depara um programa de erradicação de malária no Brasil, pois ali estão presentes condições epidemiológicas especiais relacionadas com a biologia do *A. darlingi*, com o tipo de habitações e com o modo de vida da população, ao lado do grande problema administrativo resultante da extensão da área (3 566 734 km²)[1], da baixíssima densidade demográfica (0,63 habitantes por km²) e da escassez ou ausência de meios de transporte e de comunicação, tornando quase impraticável o acesso às casas em certas regiões.

Um programa de erradicação de malária baseado no emprego de insecticidas residuais, nessa região, seria de custo proibitivo, de duração indefinida e de sucesso final muito duvidoso.

O método do sal antimalárico (método Pinotti) é muito mais indicado, em tal situação, pelos seguintes motivos:

1. A eficácia do método está sobejamente demonstrada em várias regiões do País, inclusive na região amazónica;
2. Pràticamente todc o sal de cozinha consumido na Amazónia geográfica (Estados do Pará e Amazonas, territórios federais de Rondónia, Acre, Rio Branco e Amapá) entra pela foz do rio Amazonas, a sua maior parte sendo distribuída por grandes importadores de Belém e Manaus;
3. Há certas facilidades para *contrôle* do movimento do sal e para a sua mistura com o medicamento. A maior parte do produto é importada como sal grosso, a granel, e triturada ou moída em grandes armazéns de Belém ou Manaus, antes de ensacada para venda no interior. A instalação de unidades de mistura do medicamento com o sal, antes do ensacamento deste nos armazéns referidos, constituirá a providência básica, com a qual se tratará a maior parte do sal que entra na região;
4. Embora certos problemas relacionados com o emprego do método Pinotti possam impedir a protecção inicial de todos os habitantes, estamos convencidos de que este método constitui o melhor recurso profiláctico actualmente disponível para se tentar a erradicação da malária na Amazónia brasileira. Na pior das hipóteses, o sal antimalárico exercerá inicialmente o *contrôle* da transmissão na maior parte da área, de modo mais efectivo e mais económico do que os insecticidas. Observações e estudos mais pormenorizados, a fazer no decorrer do programa, nos indicarão as providências recomendáveis para solucionar problemas eventuais relacionados com a existência de agrupamentos indígenas que não consomem sal na alimentação e outros do mesmo carácter.

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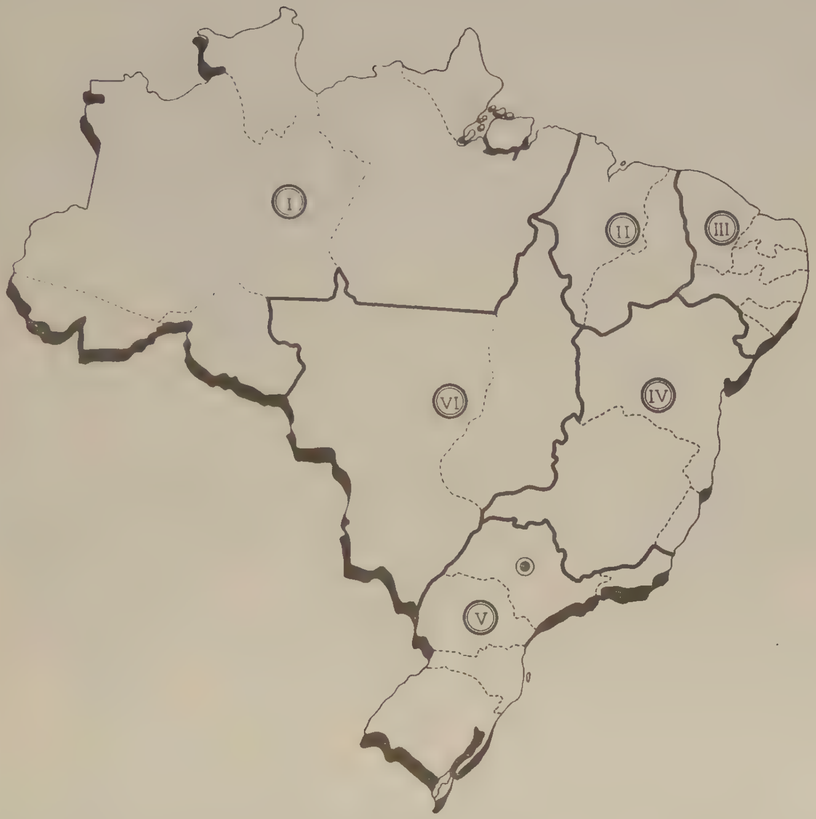
[1] Sòmente a Amazónia Geográfica.

ESQUEMA DO PLANO PARA ERRADICAÇÃO DA MALÁRIA NO BRASIL

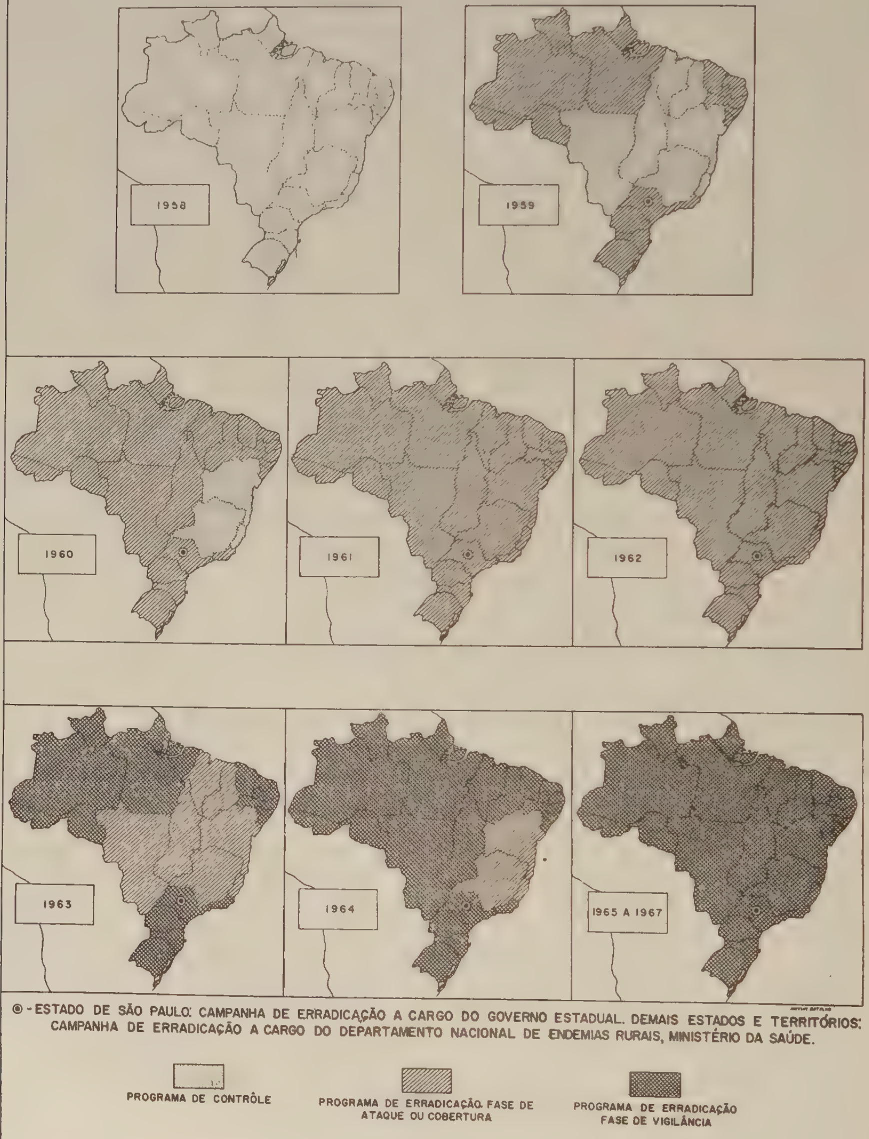


ANO	FASE PREPARATÓRIA	FASE DE ATAQUE	FASE DE VIGILÂNCIA
1958	I - III - V	-	-
1959	II - VI	I - III - V	-
1960	IV	I - III - V - II - VI	-
1961	-	I - III - V - II - VI - IV	-
1962	-	I - III - V - II - VI - IV	-
1963	-	II - VI - IV	I - III - V
1964	-	IV	I - III - V - II - VI
1965 A 1967	-	-	I - III - V - II - VI - IV

ÁREA I:- ERRADICAÇÃO COM SAL ANTIMALÁRICO (METODO PINOTTI), A SER INICIADA AINDA EM 1958. DEMAIS ÁREAS - ERRADICAÇÃO COM INSETICIDAS

◉ - ESTADO DE SÃO PAULO:- FASE DE ATAQUE OU COBERTURA A SER INICIADA AINDA EM 1958.

ESQUEMA DO PLANO PARA ERRADICAÇÃO DA MALÁRIA NO BRASIL


1958
1959
1960
1961
1962
1963
1964
1965 A 1967
PROGRAMA DE CONTRÔLE
PROGRAMA DE ERRADICAÇÃO. FASE DE ATAQUE OU COBERTURA
PROGRAMA DE ERRADICAÇÃO FASE DE VIGILÂNCIA

◉ - ESTADO DE SÃO PAULO: CAMPANHA DE ERRADICAÇÃO A CARGO DO GOVERNO ESTADUAL. DEMAIS ESTADOS E TERRITÓRIOS: CAMPANHA DE ERRADICAÇÃO A CARGO DO DEPARTAMENTO NACIONAL DE ENDEMIAS RURAIS, MINISTÉRIO DA SAÚDE.

O custo relativo do sal antimalárico, isto é, o seu custo *per capita* (Bustamante, 1958), ficará mais elevado porque de 30 % a 40 % do sal consumido não se destina ao preparo de alimentos mas a outras finalidades (salga de peixes, de carnes, de couros, alimentação de gado, etc.). Assim, o tratamento da totalidade do sal consumido encarecerá o custo *per capita* em 30 % a 40 %. Mesmo assim, entretanto, um programa com sal antimalárico baseado no custo actual, quer da cloroquina quer da pirimetamina, será sensìvelmente mais barato do que um programa com insecticidas. Deve-se considerar, ademais, a probabilidade de baixa acentuada no custo do primeiro desses medicamentos.

Os problemas relacionados com o tipo e o movimento do sal consumido na região são importantes, mas podem ser solucionados.

Em certa zona (vale do Araguaia, Estado do Pará), o sal grosso é preferido para a salga de carne, podendo este facto propiciar o consumo, pelos habitantes, de sal não tratado com o medicamento. Uma vez que as técnicas actuais não permitem o tratamento adequado do sal grosso com o medicamento, a solução desse problema poderá ser obtida com medidas legais proibindo a venda e o consumo de sal grosso na região, embora tais medidas possam ser mal recebidas pelo possível aumento de custo e, principalmente, por contrariarem hábitos tradicionais.

Outro pequeno problema é constituído pela entrada de certa quantidade de sal de mesa, refinado e de melhor qualidade que o sal moído comum. Mas esse tipo de sal, geralmente embalado em pequenos sacos ou em vasilhame de vidro, é consumido quase todo ele pelos habitantes das grandes cidades, parecendo o problema de fácil solução com algumas providências visando o tratamento na fonte abastecedora.

Enfim, certas medidas especiais terão de ser tomadas a fim de que todo o sal utilizável pelo homem seja tratado pelo medicamento e a fim de que o sal antimalárico chegue a todos os habitantes da região.

Pormenores sobre problemas relacionados com o emprego do sal cloroquinado são encontrados em outras comunicações (Paulini, 1958-*a*; Bustamante, 1959).

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ERADICATION OF MALARIA IN THE SOVIET UNION

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The Soviet Union occupies a territory which exceeds 22 million sq. kilometres. The landscape and the climatic conditions of separate regions of U. S. S. R. are extremely variable, ranging from subtropical in Transcaucasus and Central Asia to arctic in the Northern regions of the Russian Federation.

Continental climate with its high temperatures during the summer months provides conditions for the completion of sporogeny cycle of the malaria parasites and consequently for local spread of malaria disease as far as the 62° of Northern latitude. Wide river valleys rich in bogged up reservoirs of water, peatery, artificial irrigation on a vast scale and rice fields in the Southern areas of the country ensured existence for a large number of foci for mass breeding of anopheline mosquitoes.

Spread of settlements, situated as a rule along the river banks and the water reservoirs created favourable conditions for dissemination of malaria.

Severe epidemics of malaria appeared in Russia periodically in the XIX and the beginning of XX centuries. The Tsarist government had no plans for organized fight against malaria.

High incidence of malaria during the very first years after the Great October Revolution forced the Soviet Government to organize a network of special anti-malaria stations.

Upon Prof. Martsinovsky's initiative the People's Commissariat of Health organized in 1920 in Moscow an Institute of Protozoan Diseases and Chemotherapy, which is now the Institute of Malariology, Parasitology and Helminthology.

This institute was destined to become the centre of scientific research on malaria and training of specialists for anti-malaria stations for outlying areas of the country.

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During the next five years research institutes were set up in the republics of Transcaucasus and the Central Asia, which in their turn had become centres of fight against malaria. Members of the institutes formed expeditions every year that set out to study the peculiarities of epidemiology of malaria in various parts of the Soviet Union. All this served to accumulate scientific premises on which to start a planned campaign of fight against malaria.

All this research served as a base on which the associates of the institute drew up in 1934 a state plan of prophylactic measures against malaria in U. S. S. R., which was subsequently ratified by the Soviet Government.

This plan provided for a considerable increase of the anti-malaria station network and for a special annual budget and material measures to implement the plan of fight against malaria.

The plan included the following measures:

1. Examination of population inhabiting areas of malaria spread with a view of detecting the diseased and the carriers.
2. Treatment of patients applying to therapeutic institutions and of diseased individuals spotted during the examination.
3. Administration of anti-relapse course of treatment to individuals who had had malaria the previous year.
4. Destruction of malarial larvae in water reservoirs with petroleum, and by ground-sprinkling and airplane-spraying of Paris green.
5. Carrying out hydrotechnical measures in view of destroying bogged territories — the breeding places of malaria mosquitoes.
6. Mosquito-netting of houses.

In each region of the country an annual campaign against malaria was drawn up in conformity with the above lines of the general plan, and with due consideration of the local epidemiological conditions, incidence of malaria and the working conditions and peculiarities of the population. Financing and provision of medicines, insecticides and apparatus — which was and is given free to the population — is come by the local budget as well as by the All-Union budget which provides special funds for fight against malaria. A wide appeal to the population of the collectice farms and the sovkhozes was made to assist in carrying out the prophylactic measures. The application of these measures ensured a yearly decrease in malaria incidence by 20-25 % as compared to the preceding year for the country as a whole.

The Second World War had exerted a telling effect on the epidemiological conditions, causing migration of the population on a vast scale, destruction of domestic animals, disruption of drainage systems, etc. War had also upset the implementation of planned measures in numerous regions of the country.

In particular, no planned anti-malaria measures were undertaken on the territories temporarily occupied by the Germans. As a result of this, during the war years and in the years immediately after malaria incidence shot up in a number of regions. However due to the fact that the planned system was adhered to though on a reduced scale and became rapidly re-established in the liberated areas the maximum rise in the incidence of disease for the whole of the Soviet Union did not go above 30 % as compared to the pre-war figures.

The five year plan drafted at the end of 1945 as regards the fight against malaria during the period 1946-1950 provided for intensified measures in all directions. At the same time stable insecticides DDT and hexachlorane began to be used. As methods of their use became better known and they were more widely applied, the decrease in malaria incidence was accelerated starting with 1949. This permitted to tackle the problem of eradication of malaria as an epidemic disease. As the five year plan drew to its close incidence of malaria in the Soviet Union showed a five-fold decrease. In 1950 there was a 53 % decrease as compared to 1949.

The success achieved in accelerating the rate of dicrease in the incidence of malaria enabled us in 1951 to draft scientific premises for complete eradication of this disease in our country.

The general plan of malaria eradication contained two problems: This first — increase in the number of malaria-free settlements, i. e., energetic detection of diseased individuals and carriers in areas where single cases of malaria were diagnosed. Their treatment by gamotropic drugs and their outpatient clinic follow up in order to stop completely the epidemic process in such areas. The second — increase of anti-malaria measures in such regions where the incidence of disease was still high, in order to prevent its spread into the already «cleaned» regions through migration of population. To obtain rapid effect groups of specialists were sent from malaria-free areas into these regions to help the local health authorities. Such regions were offered the whole aggregate of therapeutic, prophylactic and anti-mosquito measures.

Suffice it to say that in 1956 alone 344 million of wall surface had been sprayed with DDT and hexachlorane.

To illustrate the scope of work in detecting malaria cases and carriers the following figures may be quoted.

In 1952 over 29 million people were examined, in 1953 — 23 ½ millions and, in spite of a marked drop in the incidence of malaria, over 11 million people had been examined in 1957.

These energetic measures in disease detection led to an artificial statistical delay in the decrease rate of morbidity in 1953-54, but on the other hand resulted in the acceleration of the annual rate of decrease in the following years reaching 63-66 %.

At the present time over 98 % of settlements in the Soviet Union are entirely free from malaria. In 1957 on the whole territory of the Union only 5 097 malaria patients had been registered for a population of 200 millions. In the first half of 1958 there were 1 360 cases against 2 524 patients for the same period in 1957.

The Volga basin could serve as an illustration of successful sanitation measures.

In 1950 this territory with a population of over 35 millions had 128 523 malaria cases, in 1957 — 183 cases in all, i. e., 700 times less.

Another case. In Bukhara and Samarkand regions of the Uzebekistan republic of 4 527 settlements 990 had malaria cases in 1953, i. e., 22 % of settlements were malaria-infested. In 1956 only 26 settlements had malaria cases, while in 95,4 % of settlements the disease was completely eradicated.

A third example:

If formerly construction of large water reservoirs, and hydrostations with anophilogenic shallow waters was always accompanied by on increase in malaria incidence among the population inhabiting the banks, during the construction of the Volga-Don Canal, the Gorky and Kuibyshev reservoirs malaria was completely eradicated in the adjacent regions in accordance with a special plan drafted by the engineers and the malariologists well ahead of the filling of the reservoirs with water. There was no increase in the incidence of disease after filling of reservoirs.

During the last three years a new drug, synthetized in the Soviet Union, chinocide (6-metoxy-8/4 aminopentyl/aminoquinoline-hydrochloride) was introduced for clinical use. It will cure tertiary malaria in 97-99 % of cases after a single course of treatment lasting 10-14 days.

Chinocide is used after the attacks had been arrested by any schizontotropic drug. Combined method of treatment with chinocide of every tertiary malaria case went a long way to decrease morbidity and eradicate foci of infection. Thus, during the last few years incidence of malaria decreased yearly 2,5-3 times as compared with every preceding year. Besides this the carrier rate showed a marked drop.

Two sets of measures have been designed for the period of final eradication of malaria in the Soviet Union.

Most through examination of the population to detect the malaria cases and the carriers with their subsequent treatment by using chinocide in tertiary malaria and bigumal in malaria tropica.

Outpatient control of every diseased individual for a period of 1 ½ to 2 years after diagnosis and treatment, as well as epidemiological control of the settlement where that individual lives, in order to be able to start treating fresh cases as early as possible. We consider that one of the most important measures in this direction is the examination of blood for malaria parasites in all febrile patients.

In localities where anopheles mosquito breeds the use of stable insecticides is considered mandatory. A wholesale or «barrier», or else focal treatment, as well as the treatment of cattle is carried out depending on epidemiological considerations (number of patients, the quantity of mosquitoes, migration and working conditions of the population, etc.). This sort of a double attack on the malaria focus — on the source of infection, the patient and the vector, must result, in our opinion, in more rapid and also more stable results in eradication of malaria, than the use of insecticides alone could ever furnish.

To consolidate the results achieved the Institute has drafted a special instruction on prevention of malaria in the already sanitized areas.

A special commission on the eradication of malaria in the Ministry of Health of U. S. S. R. controls all planned measures on malaria eradication including the afore-mentioned instruction. This commission delegates groups of specialists to control the work of malaria eradication and to aid the local health authorities in their work.

We hope that the implementation of the programme planned will lead to a rapid and complete eradication of fresh local cases of malaria in the Soviet Union in 1960.

After this period much work will have to be done to prevent the eruption of fresh cases of malaria. To achiev this at least two years of epidemiological control over the last eradicated foci will be necessary. Also measures will have to be taken to prevent the disease being brought from other countries where it still exists. Special international agreements will be required to solve this problem.

Translated by VICTOR P. SMOLNIKOFF, M. D., *Cand. Med. Sc.*, August 29th 1958, Moscow.

ERADICATION DU PALUDISME EN ROUMANIE[1]

Co-rapport — VIe Congrès de Médecine Tropicale et Malaria, Section 4 (Eradication du Paludisme), Division B, Lisbon, 5-13 septembre, 1958

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INTRODUCTION

La Roumanie, pays à climat tempéré et continental, situé entre 43° et 48° de latitude nord, se plaçait jusqu'à une époque récente parmi les régions très impaludés du monde.

Les différentes zones des régions endémo-épidémiques, habitées par une population de près de 6 000 000 habitants, étaient directement exposées à l'infection sur le littoral de la Mer Noire, le long du Danube et de ses affluents, dans les vallées des rivières Bega, Timiș, Criș.

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[1] Cette étude est une synthèse des recherches épidémiologiques effectuées par les paludologues et les entomologues des sections spécialisées de l'Institut Cantacuzène, en collaboration avec ses filiales et le réseau antipaludique, sous la direction du Ministère de la Santé.

Les données obtenues ont servi de base

- au mémoire présenté par M. Ciucå, L. Solomon, D. Cornelson, E. Ungureanu, G. Lupasco, E. Radacovici, M. Duport et V. Corijesco, à l'Académie de la R. P. Roumaine (Buletin Stiințific Secțiunea de Stiințe Medicale 1956, 8, nr.1) —;
- au rapport présenté par M. Ciucå, G. Lupasco, E. Ungureanu, G. Spînu et G. Maurer, à la Conférence de Paludisme, réunie à Belgrad, Yougoslavie, en décembre 1955, sous les auspices du Bureau régional de l'O. M. S.;
- au rapport présenté par M. Ciucå, G. Lupasco, D. Cornelson, L. Solo-

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Des zones intérieures de pénétration du paludisme se trouvent également jusqu'aux collines subcarpatiques dans les vallées d'érosion et les terrasses alluvionaires des affluents du Danube — (v. détails *Bull. O. M. S.* 15/725/965).

Vecteurs: L'aire de répartition des vecteurs

— *Maculipennia: A. labranchiae atroparvus, A. messeae* et *A. typicus;*

— *A. sacharovi* (elutus): à extension progressive en Dobrodgea vers le nord,

est tout aussi étendue que variée, par rapport aux conditions locales favorables au «spécifique» des: gîtes larvaires, des facteurs climatiques et de la biologie du vecteur.

On compte 5 à 7 générations du printemps jusqu'en automne.

La période favorable à la transmission pour le *P. vivax* subit de grandes variations selon la température; 115 jours environ au nord de la Moldavie; 130 dans le sud; 135 sur le littoral et le Baragan; 140 dans la vallée du Mures.

La période de transmission pour le *P. falciparum* ne dure, en général, que 27 à 44 jours au nord de la Moldavie.

Espèces de plasmodium. — La répartition quantitative des espèces du parasite comptait, en 1949, 73 % *P. vivax;* 25,5 % *P. falciparum* et 1,5 % *P. malariae.*

Ce sont les infections à *P. vivax* qui prédominent du mois d'avril au mois d'août — 80 %-90 % —; en automne le *P. falciparum* montait de 25.5 % jusqu'à 70 % pendant les vagues épidémiques de 1945/1946.

Une forte exacerbation de l'endémicité pendant la IIe guerre mondiale et les vagues épidémiques mortelles à *P. falciparum* sur le littoral en 1945/46 allaient imposer de 1947 à 1949 *une réorganisation radicale de l'action antipaludique,* basée sur de vastes études épidémiologiques

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mon, E. Ungureanu, E. Radacovici, M. Duport, M. Sândulesco, A. Agavriloaei, V. Corijesco, au Congrès National de Médecine en mai 1957;

— aux rapports présentés par la délégation roumaine à la IIIe Conférence des Pays du Sud-Est de l'Europe sur le Paludisme réunie à Bucarest — Roumanie en juin 1958 sous les auspices du Bureau régional de l'O. M. S. M. Ciucâ, G. Lupasco, E. Ungureanu, V. Corijesco et G. Constantinesco;

— au rapport rédigé par le Dr. V. Dumitresco et le Dr. V. Corijesco dans la revue «La santé publique».

et des recherches sur les méthodes «modernes» de combat dirigées conjointement:

(*a*) contre le parasite, en vue de son élimination par le traitement à l'aide des produits synthétiques à effets sélectifs, d'une part;
(*b*) contre le facteur «transmission», d'autre part, à l'aide des insecticides à effets rémanents du type D. D. T. et H. C. H.

C'est au cours de l'étape expérimentale 1947/1948[1] des nouvelles méthodes, que les premiers résultats des recherches coordonnées sur le terrain, dans les cliniques et au laboratoire, apportaient une série de faits d'application pratique sur l'efficacité et les limites de la chimiothérapie dans le «spécifique épidémiologique locale» d'action;

Les résultats acquis après 18 mois d'action antipaludique systématique montraient:

La suppression des vagues épidémiques à *P. falciparum;* la réduction de 95 % de la léthalité; une baisse de plus de 66 % de l'indice parasitaire mais, il en restait un *pourcentage de plus de 30 % de porteurs de parasites* qui nous déterminait à conclure que: (1) dans les conditions épidémiologiques et d'anophélisme local «il est indispensable d'associer d'urgence au traitment radical des cas, la méthode de désanophélisation à insecticides rémanents».

* * *

ACTION ANTIPALUDIQUE 1949-1954: ORGANISATION

En présence de la gravité de l'endémie, démontrée par l'analyse des facteurs épidémiologiques, le Ministère de la Santé procédait à la création et à la mise en oeuvre, dès 1949, d'un vaste réseau de lutte antipaludique — à action soutenue.

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[1] Arch. Roum. de Path. expérimentale t. 15/1-2/1948.

Ce réseau comptait dès le début, outre 28 stations antipaludiques complètes, 36 postes dépendants avec microscopistes et équipes mobiles, et 1 poste indépendant, éloigné des stations, répartis dans douze régions à endémie paludéenne moyenne ou intense.

Ces unités comprennent un personnel spécialisé de plus de 800 personnes, médecins paludologues, entomologistes, microscopistes, conducteurs sanitaires, chefs d'équipes, agents de désinsectisation, préparateurs, manoeuvres, etc. Elles ont été dotées de laboratoires d'hématologie et d'entomologie, ainsi que d'un équipement de lutte antianophélienne et des moyens de transport nécessaires.

Les unités spécialisées, ainsi que les unités du réseau sanitaire de base (circonscriptions, dispensaires, hôpitaux), ont reçu du Ministère de la Santé des quantités suffisantes de médicaments antipaludiqques qu'elles distribuaient gratuitement à la population. Pendant la première étape (1947-48) c'est grâce à la collaboration bénévole des infirmières de la Croix-Rouge, d'habitants des localités impaludées (instituteurs, élèves des classes supérieures) qu'on a pu donner rapidement et de façon systématique ces médicaments à un très grand nombre de malades.

Sous la direction du Ministère de la Santé le contrôle technique sur le terrain a été assumé, dès le début, par les sections spécialisées de l'Institut Cantacuzène et des Instituts d'Hygiène de Bucarest, de Jassy et de Timisoara.

PERSONNEL

Pour former un personnel qualifié, on a organisé chaque année, dès 1948, des cours de spécialisation de trois mois pour les médecins paludologues, les entomologistes et les microscopistes. On a également prévu des périodes d'instruction théorique et pratique pour les agents de désinsectisation.

Le programme de formation des médecins paludologues et des entomologistes comprend, outre des éléments d'hématologie, l'étude des protozoaires du sang, l'entomologie médicale, la clinique du paludisme, l'épidémiologie, ainsi que l'étude des méthodes de lutte et de prophylaxie; à partir de 1950, on y a ajouté des notions d'helminthologie, afin d'élargir les activités du personnel spécialisé et de lui confier d'autres fonctions au lieu de le licencier à la suite du recul de l'endémie paludéenne.

Les instituts et les sections spécialisées ont fait porter leurs efforts sur les questions suivantes: études et recherches expérimentales sur l'endémie paludéenne; amélioration des méthodes de lutte et d'investigation sur le terrain; perfectionnement du personnel spécialisé; contrôle technique des opérations: élaboration des travaux, brochures et traités spécialisés destinés à élever le niveau professionel du personnel et à éduquer le public.

ETAPES DE LA LUTTE

a. Après la période préliminaire de 1947/1948 pendant laquelle on s'est efforcé de combattre, à l'aide de la chimiothérapie schizonto-gamétocytocide systématique, les violentes vagues épidémiques mortelles qui sévissaient le long du littoral, dans la zone de Razelm-Sinoe, dans quelques localités en y ajoutant la lutte imagicide expérimentale, on a organisé le programme général de lutte antipaludique.

b. Pendant les deux premières années (1949-1950) la priorité a été donnée à l'action imagicide pour essayer d'interrompre la transmission de la maladie par l'insecte vecteur. Comme insecticides on a utilisé au bébut une solution de D. D. T. à 5 % dans le pétrole ou une solution huileuse de H. C. H. de production locale («Nitroxan») à 40 % diluée à 6,25 % dans le pétrole. Les pulvérisations étaient faites à raison de de 40 ml/m², de façon que chaque mètre carré reçut 2 g de D. D. T. pur ou 1 g de H. C. H. pur (0.30-0.37 g d'isomère gamma). Très souvent, la quantité pulvérisée variait suivant le degré de porosité des surfaces à traiter. Pendant les dernières étapes, on a employé quelquefois les produits émulsionnés (D. D. T. à 5 % préparé à partir de solutions concentrées émulsionnables à 25 %). Les appareils de pulvérisation étaient du type Calimax à pression à main, d'une capacité de 12 litres. A l'intérieur des habitations, on a traité les parois jusqu'à une hauter de 1 mètre à partir du plancher ainsi que toutes les encoignures, fentes et rainures. On s'est appliqué tout particulièrement à désanophéliser les abris d'animaux, les gouttières et les bords des toits de roseaux. On vérifiait de temps à autre l'efficacité des produits par le test biologique (exposition expérimentale des anophèles à l'insecticide pendant 60 minutes), ainsi que par le contrôle de la densité anophélienne effectué périodiquement jusqu'à six mois après les pulvérisations de D. D. T. et deux mois et demi à trois mois après celle d'H. C. H.

Quant à l'effet rémanent du H. C. H. — l'insecticide le plus utilisé — on a constaté que les villages traités présentent par rapport aux villages témoins, une densité anophélienne toujours faible, même 50-70 jours après la fin des pulvérisations.

Toutes les opérations de désinsectisation ont été fondées sur une étude scientifique de l'anophélisme dans le pays: observations phénologiques, densité des adultes et des larves, variations saisonnières des espèces.

Si l'on considère la durée de la transmission dans notre pays (4-5 mois) et la durée de la toxicité pour l'anophèle des insecticides utilisés (D. D. T.: 6 mois; H. C. H.: 2 ½-3 mois), une seule désinsectisation par an, deux semaines avant l'eclosion de la première génération d'anophèles, assure en général une protection suffisante contre les vecteurs.

Le nombre des localités désinsectisées a varié chaque année: la surface traitée a progressivement augmenté. Alors qu'elle était d'environ 58 millions de mètres carrés, elle a passé de 1949 à 1951, à plus de 80 millions de mètres carrés. En 1952, elle atteignait encore environ 70 millions de mètres carrés (voir tableau 1).

TABLEAU 1 — *Type de traitements imagicides effectués en Roumanie de 1949 à 1954*

Année	Nombre de localités traités	Traitement			Surface traitée (Km²)
		Intégral	En barrière ou partiel	En foyer	
1949	668	656	12	—	57.790
1950	777	772	5	—	76.191
1951	848	841	7	—	81.626
1952	727	713	9	3	70.626
1953	787	668	60	59	66.676
1954	745	604	98	43	58.752

Dès les premières pulvérisations (1949-1950) on a enregistré une forte baisse de la morbidité par paludisme.

Parallèlement, on a traité systématiquement les cas de paludisme par les schizontocides et les gamétocytocides et on a appliqué la chimioprophylaxie à certains groupes de la population exposés à l'infection.

c. Pendant les années 1951-1952 on a cherché à améliorer et à conosolider les résultats obtenus par la désinsectisation et en même temps on a renforcé la méthode de lutte contre l'infection chez l'homme. Déjà se dessinaient les lignes générales du nouveau plan de lutte antipaludique en vue d'une élimination du paludisme à l'avenir. Le personnel qui travaillait sur le terrain a reçu alors de nouvelles instructions: il devait dépister et enregistrer les cas avec plus de rapidité et d'exactitude, confirmer le diagnostic par des examens de laboratoire répétés et faire suivre le traitement schizontocide d'un traitement clino-prophylactique — pendant toute la saison paludique (Avril-Octobre).

d. Au cours des années suivantes (1953-1954) on a supprimé la désanophélisation imagicide intégrale dans un certain nombre de localités qui avaient été traitées pendant les trois ou quatre années précédentes et où la morbidité avait baissé et restait faible — 1 ou 2 cas. Mais, autour de ces localités, on a établi une zone de protection que l'on continuait à traiter aux insecticides. Dans les localités où l'impaludation est restée intense, les désinsectisations massives ont été poursuivies; ailleurs, où elle était moins forte, on a employé la méthode de la désanophélisation «en foyer» et autour du foyer, autrement dit on a traité l'habitation du paludéen et les maisons les plus proches.

D'autre part, le traitement destiné à l'élimination définitive du parasite (guérison radicale), qui avait déjà été appliqué en 1952, a été étendu à tous les paludéens.

Les résultats des «méthodes combinées» d'action dirigées en vue de l'élimination des parasites par la thérapie et de supprimer la transmission par les insecticides ont été *la diminution progressive du paludisme* (voir tableau 2 et graphique annexe).

Tableau 2 — *Morbidité par paludisme en Roumanie de 1948 à 1954*

Cas	1948	1949	1950	1951	1952	1953	1954	Diminution en 1954 par rapport à 1948	
								en nombres absolus	en pourcent
Nouveaux ..	210.111	168.552	55.175	24.430	4.833	1.130	542	209.569	99.72
Rechûtes	128.087	65.410	40.294	17.598	5.616	1.990	361	127.726	99.72
Total ...	338.198	233.962	95.469	42.028	10.449	3.120	903	337.295	99.73

A la fin de l'année 1954, la morbidité paludéenne était pour tout le pays de 5,3 pour 100 000 habitants. A cette date on enregistrait une *incidence de 903 cas* de maladie, dont *542* nouveaux et *361* rechutes.

Sur le territoire des régions munis de Stations antipaludiques et «points dépendants» — presque toute la zone endémique du pays — le nombre des lames positives a été de 361 sur 86.937 lames examinées.

PROGRAMME D'ERADICATION 1955

En Avril 1955, en présence des «valeurs exceptionellement réduites» du paludisme dans le pays et en tenant compte des opérations préparatoires déroulées par l'organisation et l'action antipaludique des années précédentes 1948-1954, les malariologistes roumains prenaient la responsabilité de recommander — dès 1955 — l'introduction du programme d'éradication à grande échelle passant directement à la «*phase d'attaque*». Le nouvel objectif a été adopté par le Ministère de la Santé et de la Prévoyance Sociale et les plans d'action ont été transmis aux unités opératives.

Les lignes générales du programme national d'éradication du paludisme sont les suivantes:

1) Les principes et les méthodes de lutte seront fondés sur de nombreuses recherches épidémiologiques et adaptés aux particularités locales de la biologie, de la bionomie et de la phénologie des vecteurs dans les régions désanophélisées ou non, dans celles où l'on a remplacé la désinsectisation en masse par la désinsectisation «en foyer» et dans celles où le paludisme est déjà éliminé et qui sont protégées par des barrières d'insecticides.

2) La recherche d'éventuelles souches résistantes d'anophèles sera faite systématiquement à l'aide de tous les tests existants. Elle portera sur un très grand nombre d'insectes capturés dans les différentes régions énumérées plus haut.

3) Un an avant d'interrompre complètement la désinsectisation dans une zone — où l'on avait abandonné la désinsectisation en masse pour les pulvérisations «en foyer» — on effectuera un contrôle clinique et hématologique de toute la population et l'on protégera la zone par de larges barrières d'insecticides.

4) Afin que l'on puisse interrompre les pulvérisations d'insecticides, avant que la résistance n'apparaisse chez les vecteurs, on appliquera les méthodes les plus rigoureuses de dépistage et de contrôle épi-

démiologique et l'on administrera systématiquement à tous les malades et porteurs de parasites le traitement curatif complet.

5) Pendant toutes les opérations, on évitera les doses sub-léthales d'insecticides, qui sont les plus favorables à l'apparition de la résistance. A cet effet, on assurera au maximum la bonne conservation et la standardisation du principe actif de l'insecticide. Mieux vaut en tout cas utiliser des doses trop fortes que des doses trop faibles.

6) Autour des régions où le paludisme est déjà éliminé, on élargira progressivement les barrières d'insecticides jusqu'aux frontières nationales et même au delà, après entente avec les pays limitrophes.

Pour ne pas perdre le fruit de la victoire et supprimer à tout jamais le paludisme dans le pays, il faut encore renforcer les cadres du personel qualifié et assurer une étroite collaboration entre les membres de ce personnel. La surveillance épidémiologique doit être constante; les médicaments antipaludiques et les insecticides doivent être produits en grande quantité et répondre aux normes recommandés par le Comité d'Experts des Insecticides de l'O. M. S.

Ainsi, s'il apparaît de nouvelles souches d'anophèles résistantes, l'homme sera en mesure de se défendre.

SITUATION GÉNÉRALE DU PALUDISME PENDANT LA «PHASE D'ATTAQUE»

Au cours des trois premières années (1955-1957) de la «phase d'attaque», pour une population totale de 17 000 000 habitants on n'a enregistré qu'un total de *570 cas de malaria* confirmés par examen hématologique, en général des cas sporadiques 1-2 par localité et seulement quelques microfoyers résiduels de 4 à 8 cas. La régression est marquée dans le tableau 3 qui suit, ainsi que dans le graphique annexe.

La carte de la répartition topographique du paludisme pour la période respective, montre que la majorité des localités appartiennent à quelques anciens territoires endémiques et voisins de ces derniers; on a dépisté toutefois des cas en dehors de ces zones de contrôle.

Une proportion réduite des cas, avec une légère hausse par rapport aux années précédentes provient en 1956 et 1957 de certains territoires traités auparavant à l'aide de substances insecticides rémanentes.

TABLEAU 3 — *Incidence du paludisme en Roumanie (1955-1957)*

	Année	Population	Cas confirmés hématologiquement	Observations
	1955	17.325.000	222	
	1956	17.489.000	184	
	1957	17.767.485	164	
Organisation de la surveillance active	1958 (pour 6 mois)	1.500.000	170	Données provisoires

Dans les régions sous le contrôle des Unités spécialisées antipaludéennes, les cas confirmés, après examen hématologique de 278 612 lames de sang, appartenaient aux malades «suspects», febriles et sous-fébriles, ainsi que ceux provenant du contrôle des «foyers» où l'on pratiquait des investigations épidémiologiques (tableau 4).

TABLEAU 4 — *Examens hématologiques effectués par les Stations et «Points» de lutte antipaludique*

Année	Lames examinées	Positives		Espèces d'hématozaires			
		Chifre	%	*P. vivax*	*P. falciparum*	*P. malariae*	F. associées
1955	89.800	222	0.24	210	10	2	—
1956	101.311	179	0.17	141	29	6	3
1957	87 501	164	0.18	139	14	11	—

Pendant les premières deux années plus de la moitié du total des gouttes épaisses positives étaient «concentrées» dans le bassin hydrographique *rigoureusement surveillé du «Vedea-Teleorman»*, Région de Bucarest (v. charte), où l'on avait également enregistré ⅔ des infections ou *P. falciparum* en 1956.

L'incidence des cas dans ce principal foyer endémo-épidémique a enregistré une continuelle regression pendant l'intervalle 1954-1957, respectivement de 209, 129, 110 et 71 cas; en 1958 l'organisation et la mise en oeuvre de la *surveillance active décèle de 1.I — 30.IV — 67 cas.*

EFFICIENCE ET CRITIQUE DES MÉTHODES DE CONTRÔLE UTILISÉES

Pendant l'intervalle 1955-1957, l'action antipaludique s'est déroulée sur la base des principes généraux suivants:

a) Dépistage des cas par examens hématologiques répétés des suspects; contrôle des fébriles et sous-fébriles; enquêtes et investigations épidémiologiques des «foyers»;

b) «Neutralisation» du point de vue épidémiologique de chaque cas par la double méthode:
  - Élimination du parasite par cure radicale à l'aide d'un traitement rigoureux;
  - Suppression de la transmission à l'aide d'insecticides.

c) Contrôle de la rémanence des insecticides;

d) Tests de la sensibilité des anophèles aux insecticides employés;

e) Mesures de protection antipaludique — *différenciées* — dans les zones d'accord avec les Républiques Populaires Bulgare et Yougoslave.

Dans le cadre des mesures de détails, des efforts soutenus ont été tout particulièrement portés dans l'application des «méthodes primaires» utilisées, à voire:

1. Chimioprophylaxie suppressive des «anciens cas»: traitement complet schizonto-gamétocide suivi de doses hebdomadaires suppressives des «nouveaux cas» au fur et à mesure de leur apparition et enregistrement. Les cas suspects — malades à symptomatologie clinique — ont reçu seulement le traitement schizontocide (en attendant les résultats du laboratoire).

2. *Les opérations imagicides* — pulvérisations intégrales — se sont limitées généralement aux localités pulvérisées dans les années précédentes et la suppression des opérations dans quelques-unes des localités *n'a pas été toujours assurée par une extension territoriale satisfaisante aux alentours.*

Pendant les trois dernières années on a pratiqué aussi des désanophélisations en «foyer» et «barrières» — mais la méthode a été *insuffi-*

samment employée par rapport aux foyers où elle a été appliquée, parfois avec des retards saisonniers ou dans un nombre réduit d'habitations.

Des défections administratives temporaires ont prolongé par endroits les pulvérisations aux insecticides au delà de l'intervalle utile pour qu'elles soient entièrement efficientes à l'interruption de la transmission. On en trouve la preuve dans les 37 localités — traitées «anti-imago» — où l'on y avait enregistré 83 cas de malaria en 1956 et 70 autres cas secondaires en 1957.

Les chiffres des surfaces murales traitées dans tout le pays totalisaient: 66 669 000 m^2 en 1955; 66 669 000 m^2 en 1956 et 72 950 000 m^2 en 1957.

La population des collectivités traitées totalisait: 1 164 000 personnes dont 839 000 protégées directement en 1955; 1 555 000 dont 980 000 protégées directement en 1956 et 1 466 000 dont 866 800 protégées directement en 1957.

RECHERCHES SCIENTIFIQUES DE BASE

L'activité antipaludique est constamment basée, dans notre pays, sur des investigations et des recherches scientifiques fondamentales imposées par la complexité même des conditions et des facteurs épidémiologiques locaux, spécifiques à chaque pays.

Des études concernant:

- La biologie des souches locales de parasites;
- La biologie et l'écologie des vecteurs locaux de l'infection par rapport aux facteurs épidémiologiques locaux, utilisaient, en même temps, largement les progrès des découvertes et de l'expérience acquise au cours des dernières 15 années dans le domaine de la lutte antipaludique sur le plan mondial.

Les principales problèmes à l'étude sont:

A. La susceptibilité et la tolérance des vecteurs locaux aux insecticides remanents utilisés;
B. L'efficacité de la chimiothérapie à l'aide des nouveaux médicaments antipaludiques de synthèse — pyriméthamine, prima-

quine et chinocide — par rapport à la biologie des souches locales de parasites.

Ces recherches sont inscrites dans le programme plus vaste des «recherches coordonnées» effectuées parallèlement dans plusieurs pays et différents Instituts nationaux et dirigées par l'O. M. S. (v. annexe 1).

RECOMMANDATIONS POUR LE DÉVELOPPEMENT DU PROGRAMME D'ACTION POUR 1958 (ET LES ANNÉES SUIVANTES)

La réalisation de l'éradication est subordonnée aux conditions suivantes:

- Intensification du dépistage des cas et des microfoyers résiduels du paludisme;
- Traitement rigoureux des cas et des suspects;
- Intensification des opérations d'attaque par des pulvérisations totales d'insecticides exécutées en temps utile partout où la transmission est évidente ou bien représente un réel danger.

A cette fin il est donc nécessaire pendant l'année en cours et les trois années à venir, de définir les méthodes et d'en préciser les modalités d'application:

- Surveillance passive sur tout le territoire du pays et surveillance passive et *dépistage actif des cas* dans les anciennes zones endémiques du paludisme.

En vue de «l'élimination du parasite», les mesures suivantes sont nécessaires:

- Contrôle périodique (clinique et de laboratoire) des malades confirmés, des «suspects» et des anciens impaludés et leur traitement radical;
- Contrôle sévère des donneurs de sang et surtout de ceux provenant des zones endémiques;

- — Pulvérisations intégrales dans les localités où l'on a constaté des signes de transmission active du paludisme au cours des trois dernières années, ainsi que celles situées à moins de 10 km des précédentes;
- — *La suppression des pulvérisations* des localités où le paludisme a été éliminé au cours des trois dernières années *sera subordonnée à l'existence d'un système rigoureux de «surveillance épidémiologique active et passive»*.

Au cours de l'exécution du programme d'éradication, il est nécessairement obligatoire de préciser «l'origine des cas», c'est-à-dire s'ils sont indigènes ou importés ainsi que d'appliquer des mesures adéquates pour chaque cas — suspect ou confirmé.

L'exécution de ces mesures incombe *à tous les services du réseau sanitaire de base à tout le personnel médical et sanitaire — du pays*.

Les services spéciaux du réseau antipaludique suivront strictement l'exécution des opérations de pulvérisation au cours des 2 premières mois de la saison de transmission — 15 Avril-15 Juin — (1 Juillet dans le nord du pays).

Des opérations «exceptionnelles» au cours des mois suivants sont prévues dans les éventualités suivantes:

- — Diminution de l'effet toxique, rémanent des insecticides ou
- — Détection de nouveaux cas — hématologiquement confirmés — dans les localités non-traitées, au cours de la période 15 Juin-1er Octobre, ou même plus tard.

On s'efforcera tout spécialement de vérifier et de préciser les causes de l'inefficacité des opérations entreprises pour supprimer la transmission:

- — Qualité et standardisation de l'insecticide;
- — Manque d'efficacité de l'insecticide ou des méthodes employées; saison d'application de ces insecticides, etc.;
- — Éventuelle apparition de la résistance physiologique aux insecticides;
- — Facteurs locaux inhibiteurs relevant des habitations et du milieu, etc.

Le Ministère de la Santé et des Prévoyances Sociales procède à l'élaboration d'une législation relative aux mesures antipaludiques à prendre pendant l'application du programme d'éradication.

Recherches coordonnées — En 1958 on donnera l'extension nécessaire — par rapport au matériel biologique disponible — aux recherches — en voie d'exécution — effectuées sous la Direction scientifique de l'Institut I. Cantacuzène et sous les auspices et avec l'aide de l'O. M. S.:

a) Sensibilité et tolérance des vecteurs locaux aux insecticides, évaluées par les méthodes standardisées O. M. S.

b) Recherches de la chimiothérapie:

— Action sporontocide et effets thérapeutiques de «guérison radicale» à l'aide des nouveaux produits antipaludiques.

CONCLUSIONS

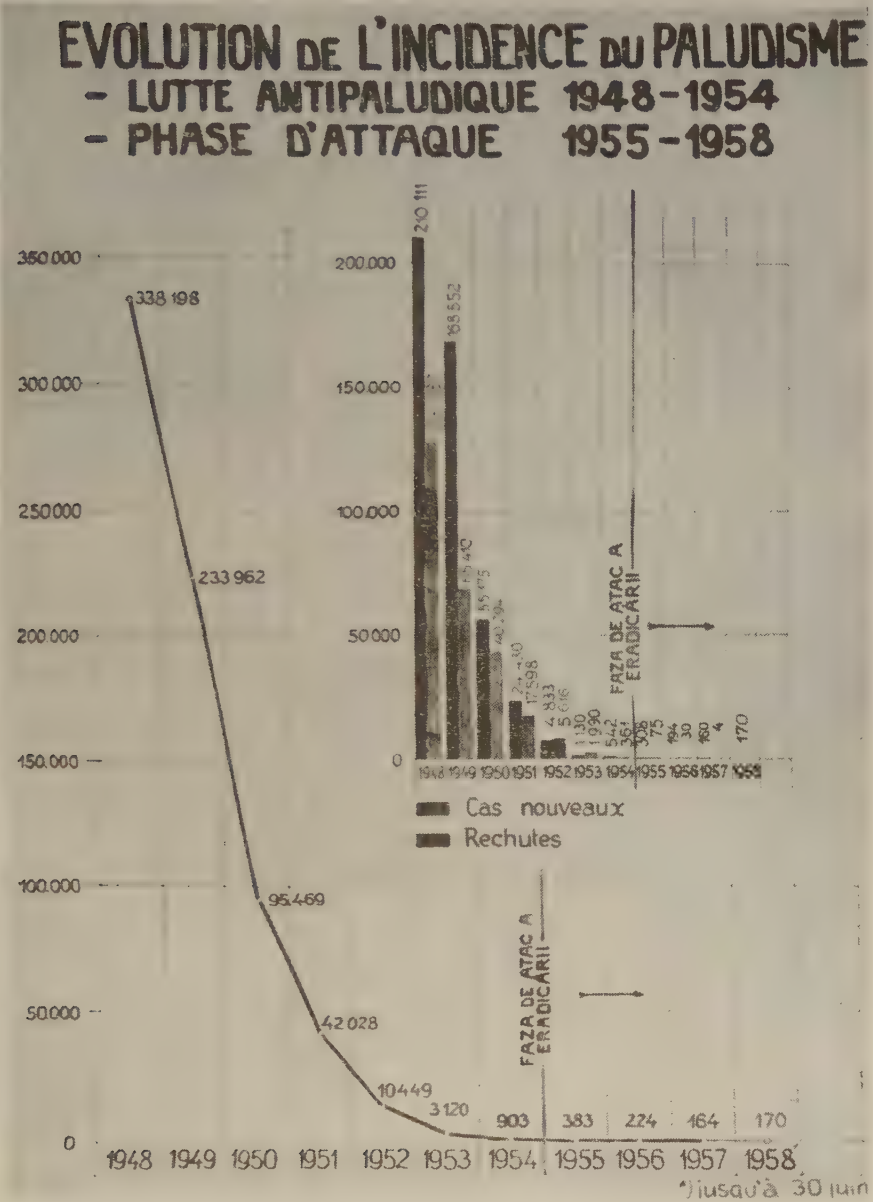
Les opérations de la phase d'attaque, étendues sur toutes les zones d'endémicité, seront continuellement améliorées — sans leurs fixer leurs durée en années — jusqu'à l'élimination définitive des cas sporadiques et des microfoyers «autochtons» à l'aide d'une surveillance active et passive parfaite effectuées avec la collaboration de tout le réseau sanitaire du pays, et de la désinsectisation intégrale des localités d'origine.

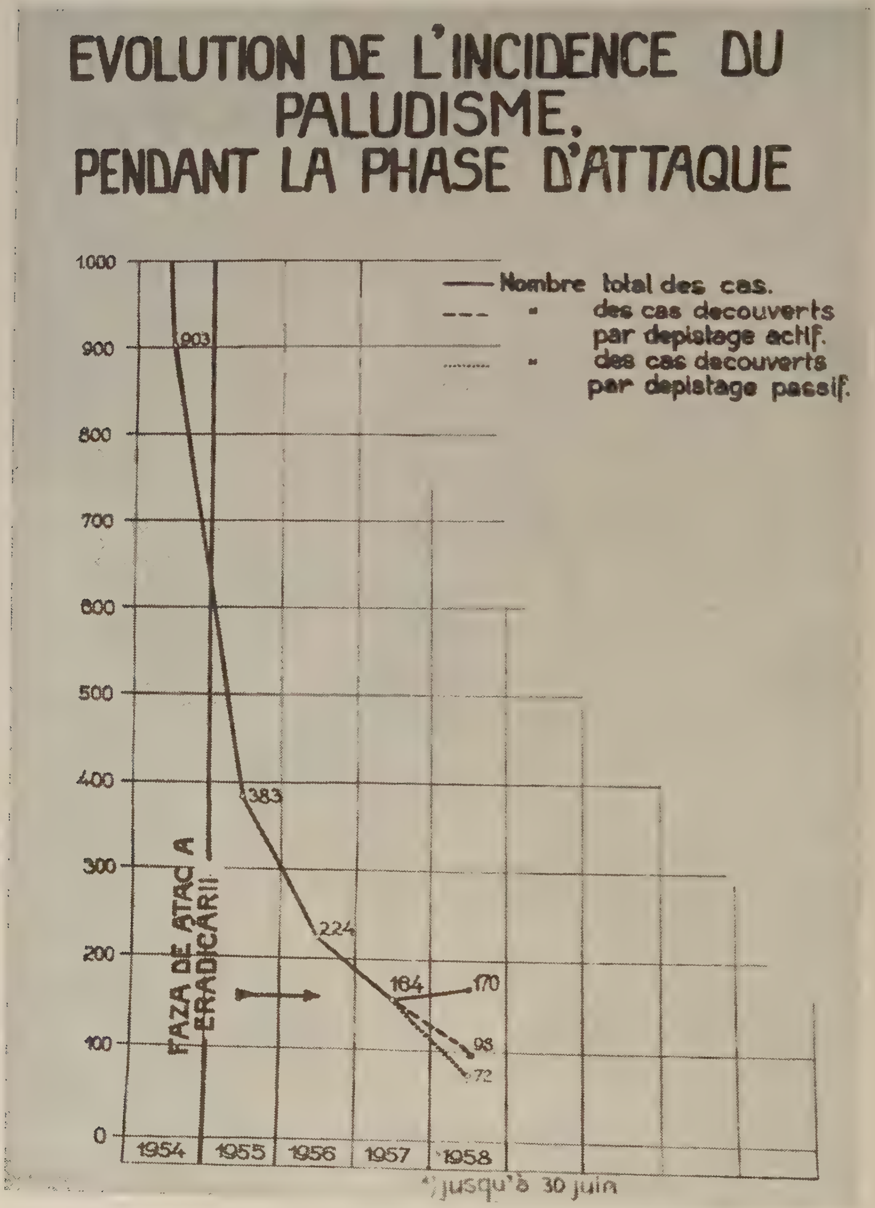
L'intensification, pendant le développement du programme «d'éradication» des recherches et des investigations de caractère permanent, concernant:

a) L'élimination de la transmission et l'efficience de la rémanence des insecticides; la susceptibilité et la tolérance des vecteurs, d'une part;

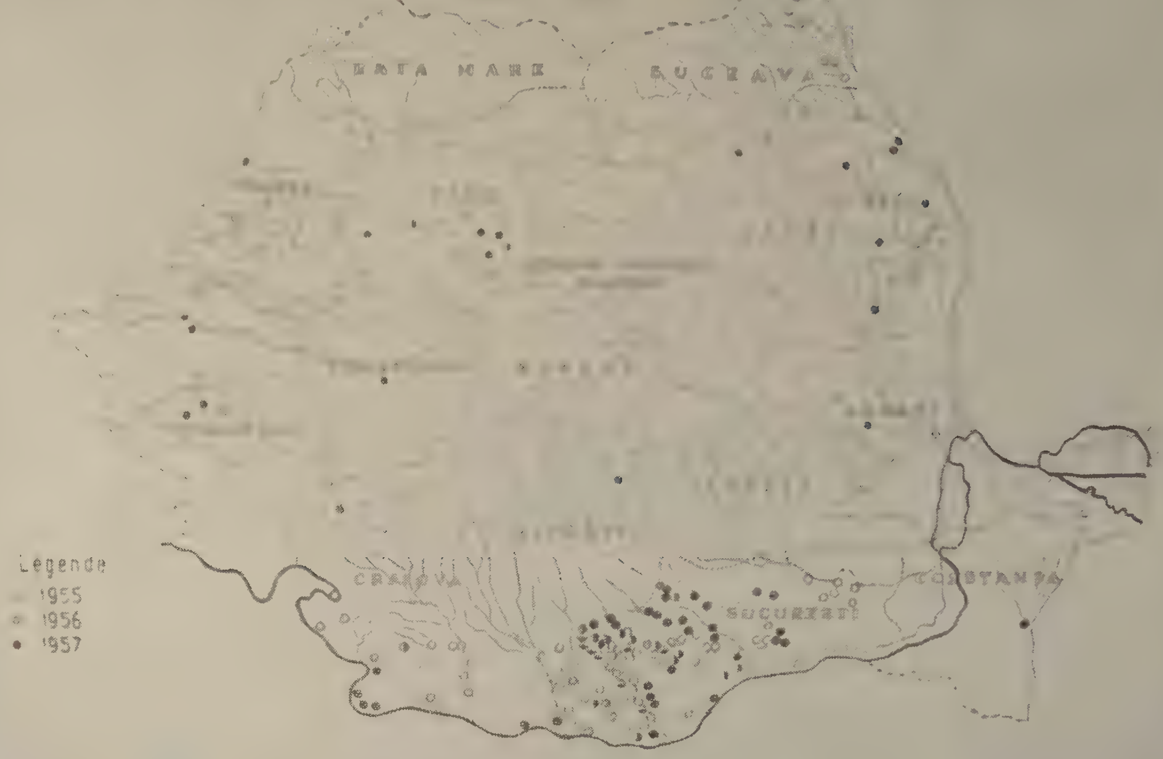
b) La susceptibilité et éventuellement, la résistance des souches locales de parasites aux différents produits antipaludiques des groupes 4-8 aminoquinoleines, biguanide et dyamino-pyrimidine, — d'autre part.

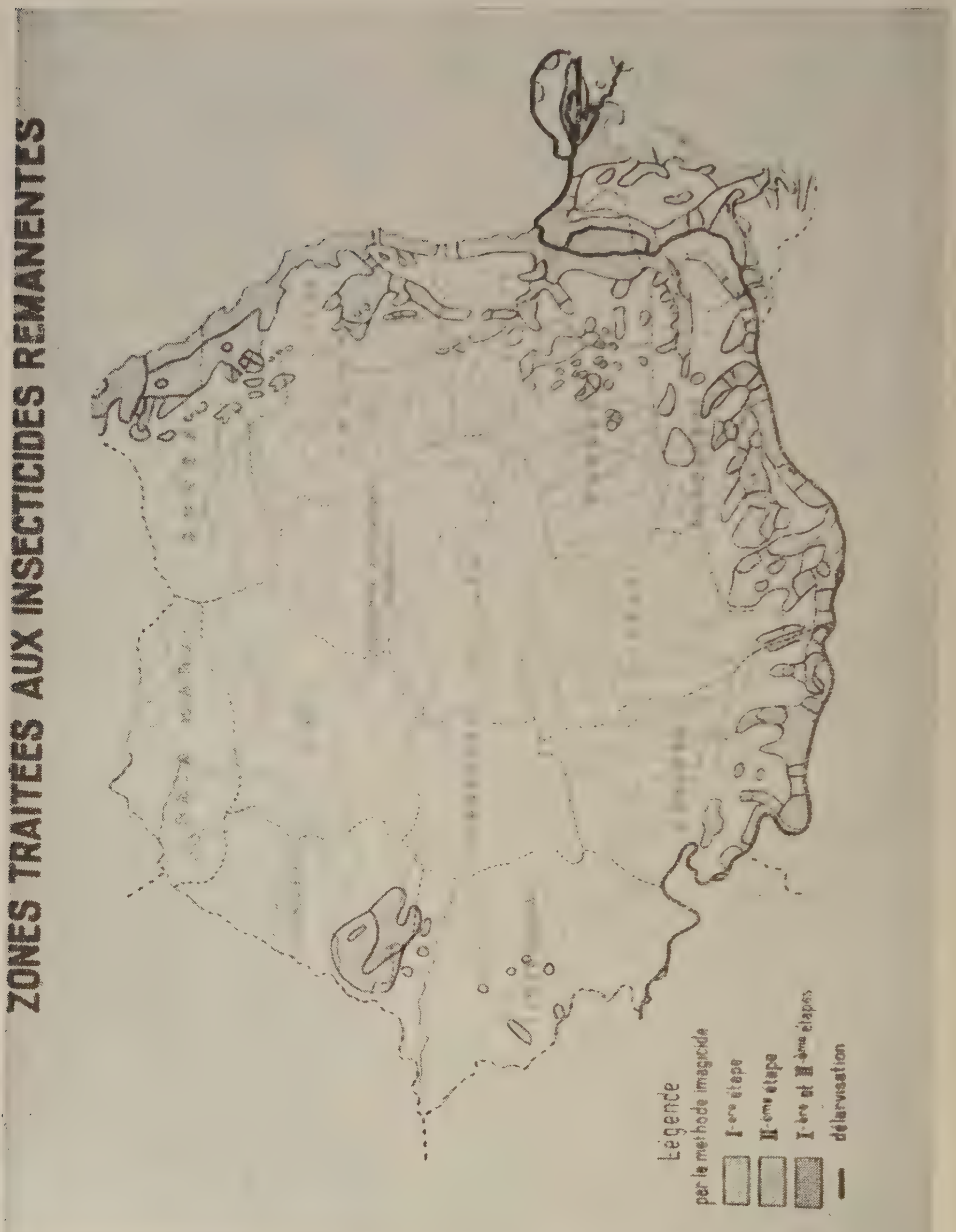
Compléter d'urgence les accords bilatéraux avec tous les pays limitrophes et intensifier au maximum les échanges d'information épidémiologiques, d'expérience et de documentation méthodologique.

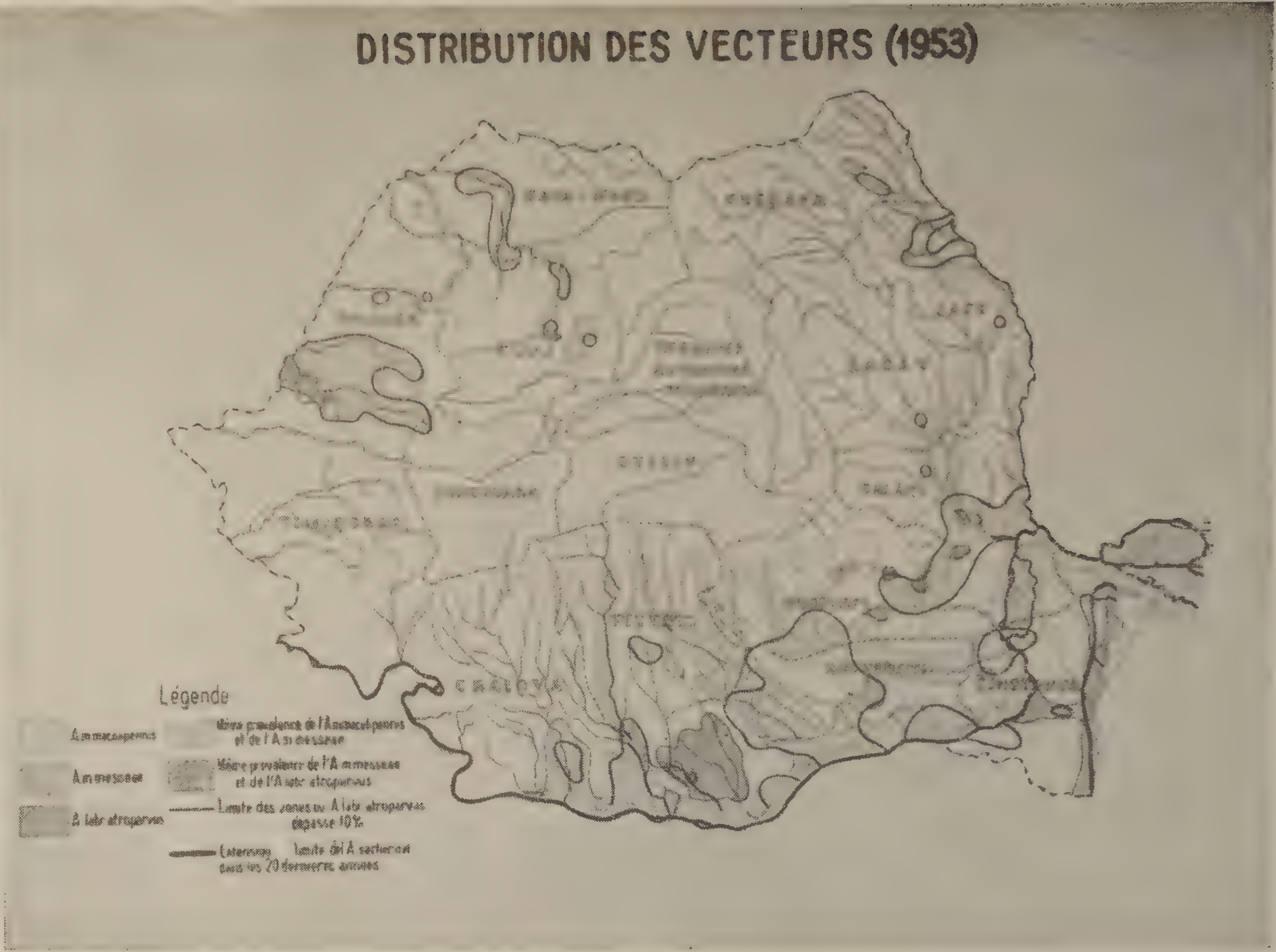

EVOLUTION DE L'INCIDENCE DU PALUDISME
- LUTTE ANTIPALUDIQUE 1948-1954
- PHASE D'ATTAQUE 1955-1958
350.000
300.000
250000
200.000
150.000
100.000
50000
0
338 198
233 962
95.469
42 028
10449
3 120
903
383
224
464
170
FAZA DE ATAC A ERADICĂRII
1948 1949 1950 1951 1952 1953 1954 1955 1956 1957 1958*
*) jusqu'à 30 juin
200.000
150.000
100.000
50000
0
210 111
168 552
55 475
17598
4 833
5 616
1 130
1 990
542
361
308
75
30
4
170
FAZA DE ATAC A ERADICĂRII
1948 1949 1950 1951 1952 1953 1954 1955 1956 1957 1958
Cas nouveaux
Rechutes


EVOLUTION DE L'INCIDENCE DU PALUDISME, PENDANT LA PHASE D'ATTAQUE
1.000
900
800
700
600
500
400
300
200
100
0
Nombre total des cas.
" des cas decouverts par depistage actif.
" des cas decouverts par depistage passif.
903
383
224
164
170
98
72
FAZA DE ATAC A ERADICĂRII
1954
1955
1956
1957
1958
*) jusqu'à 30 juin

LOCALITÉS DANS LESQUELLES DES CAS CONFIRMES DE PALUDISME ONT ÉTÉ NOTIFIÉS PENDANT LES ANNÉES 1955-1957


BAIA MARE
SUCEAVA
CRAIOVA
BUCUREŞTI
CONSTANŢA
Legende
1955
1956
1957


ZONES TRAITEES AUX INSECTICIDES REMANENTES
Légende
par la méthode imagocide
I-ère étape
II-ème étape
I-ère et II-ème étapes
délarvisation


DISTRIBUTION DES VECTEURS (1953)
CRAIOVA
Légende
A. m. maculipennis
A. m. messeae
A. labr. atroparvus
Mixte prévalence de l'A. m. maculipennis et de l'A. m. messeae
Mixte prévalence de l'A. m. messeae et de l'A. labr. atroparvus
Limite des zones où A. labr. atroparvus dépasse 10%
Extension limite de l'A. sacharovi dans les 20 dernières années

MALARIA ERADICATION IN THE UNITED STATES

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Detailed accounts of purposeful efforts and incidental developments leading to the drastic curtailment of endemic malaria in the United States have been presented elsewhere (1). Accordingly, I shall review briefly only the more pertinent facts as a prelude to a discussion of the present status of malaria in our country. Some of the circumstances involved are indicated on figure 1 in relation to reported malaria morbidity and mortality in the United States since 1932. This period includes the mid-thirties epidemic, the last of national significance (2).

It seems to be an historic fact that malaria pervaded the life of most of the American colonials and frontiersmen, by whom it was disseminated widely throughout the country (3, 6). The disease localized wherever vectoral species of anophelines were abundant and had access to man, and where favorable ambient temperatures were sustained long enough to complete sporogony in mosquitoes. With the development of increasing urbanization, improved agricultural and right-of-way practices, and better housing, the previously extensive areas of endemicity contracted to the southeastern coastal plains, the south central fluvial plain, and certain river valleys and irrigated sections in California and New Mexico (2, 7).

This notable decrease in the affected terrain must have reduced the occurrence of malaria on a national basis, but the disease continued to be of enormous significance in the remaining endemic regions of the country. As late as 1938, just two decades ago, L. L. Williams, Jr., eminent malaria authority of the U. S. Public Health Service, estimated

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on the basis of his experience and observations that as many as four million individuals were afflicted year after year, with this number increased by fifty per cent or more in epidemic years — and that the annual cost of the disease was not less than five hundred million dollars (8).

Factors which influenced the downward trend of malaria prevalence since its last exacerbation include the activities of malaria survey-and--control organizations in the southeastern State health departments, the development and application of improved antilarval practices in water impoundments in the Tennessee River Valley and elsewhere (9, 10), extensive minor and major drainage by relief labor organizations (Civil Work Administration, Federal Emergency Relief Administration, and Works Progress Administration) (11, 12).

During World War II, anti-mosquito measures were practiced on all military establishments as needed. Coordinated with these activities in traditionally malarious areas were similar procedures directed specifically against malaria-carrying species of mosquitoes within flight range of military and was industry areas. These were carried on by State Health Department malaria control personnel with the assistance and coordination of the newly formed (1942) Malaria Control in War Areas organization of the U. S. Public Health Service (13). This extracantonmental War Areas Program was instituted originally for the protection of military trainees and war industry workers against malaria from civilian sources. Later, as wounded service men, prisoners of war, and demobilized veterans were sent to the States from malarious areas overseas, the same antianopheline practices were continued (Extended Program) for the protection of U. S. civilians against imported strains of malaria. These were shown by Young and his coworkers (14) to be as infectious to Americans as were the indigenous strains. The increased malaria morbidity from relapsing cases acquired overseas appears in figure 1 as a conspicuous hump in the case number graph from the years 1944 to 1947. With this exception, the numbers of cases and deaths continued to decline.

This series of circumstances encouraged the conviction, already expressed by Dr. Williams in 1944 (15), that malaria could be eradicated from the United States. Plans were developed and budgetary proposals to that effect were put before the U. S. Congress in 1946 (1). These were implemented promptly and in 1947 the National Malaria

Eradication Program was begun by the U. S. Public Health Service in cooperation with the State and local health departments involved. These activities were coordinated by the Communicable Disease Center, successor in 1946 to the Malaria Control in War Areas organization, and with similar but broader responsibilities (16).

The program (1) consisted primarily of semi-annual, later annual, spray applications of D. D. T. in houses in rural areas of counties selected according to previously reported malaria mortality. The effectiveness of these insecticidal operations was evaluated by counts of mosquitoes resting in sprayed and unsprayed houses. To stimulate and assess good malaria case reporting and to determine the probable origin of new cases, teams composed of a medical or nurse epidemiologist, an entomologist, and a sanitary engineer or an insect control specialist were assigned to State health departments where the probability of transmitting reintroduced malaria seemed relatively great.

As a basis for making administrative decisions regarding the continuance or termination of the program, the National Malaria Society developed criteria for determining when malaria was eradicated (17). These stated that «malaria may be assumed to be no longer endemic in any given area when no primary indigenous case has occurred there for three years, if reporting and case finding are actively promoted and adequate investigations are carried out». Primary indigenous malaria was defined as an initial, parasite-positive attack, i. e. not a relapse, of malaria resulting from natural (mosquito) transmission in the given area. Adequate investigation was described as the epidemiologic investigation and appraisal of each reported case by qualified personnel, involving the verification of the diagnosis, and determining, if possible, where and when the transmission occurred. It was recommended that all blood films considered positive be submitted to a national depository — the Communicable Disease Center — designated for that purpose. Comparable criteria of cessation of transmission have been proposed by the Expert Committee on Malaria of the World Health Organization (18).

The decrease in numbers of reported cases and deaths was maintained as shown in figure 1, until after 1950, when the former rose sharply. This resulted from the evacuation to the States of casualties and other combatants exposed to vivax malaria during the invasion of South Korea (19) who developed initial attacks or relapses some time after suppressive medication with chloroquine was discontinued. The reported case numbers shown in figure 1 are far short of the actual numbers of relapsing cases as , according to Archambeault (19) there were 13,483 cases of malaria in 1951 and 12,346 in 1952 among military personnel on active duty in the United States.

Because of this extraordinary and threatening experience, a U. S. Army Mission was dispatched to the Far East Command during the summer of 1951 to explore the feasibility of using primaquine (20) to cure latent malaria while servicemen were making the two-weeks voyage home on transport vessels. Controlled field trials conducted in Korea (21) and in the United States (22), and clinical observations made aboard transports (12) clearly established the relative safety and effectiveness of 15 mg of primaquine base taken daily for 14 days on shipboard. Accordingly, this regimen was ordered for all troops returning from Korea by transport. This was not effectively implemented until the summer months of 1952 (19).

A study by Archambeault of records of administration shows that the procedure was both feasible and effective (19). Toxic reactions were few. Malaria morbidity in military personnel fell off sharply in 1953, and this is clearly reflected in figure 1 which includes cases of malaria reported from civilian sources only. The vast majority of these were veterans with service in Korea or other malarious areas. The sucessful development and large-scale application of primaquine therapy to minimize the importation and re-establishment of malaria into receptive areas is a truly remarkable addition to the armamentarium of the malariogist. It encourages the hope that chemotherapy, as well as insecticidal technology, may play an increasingly decisive role in the control and eradication of paludism.

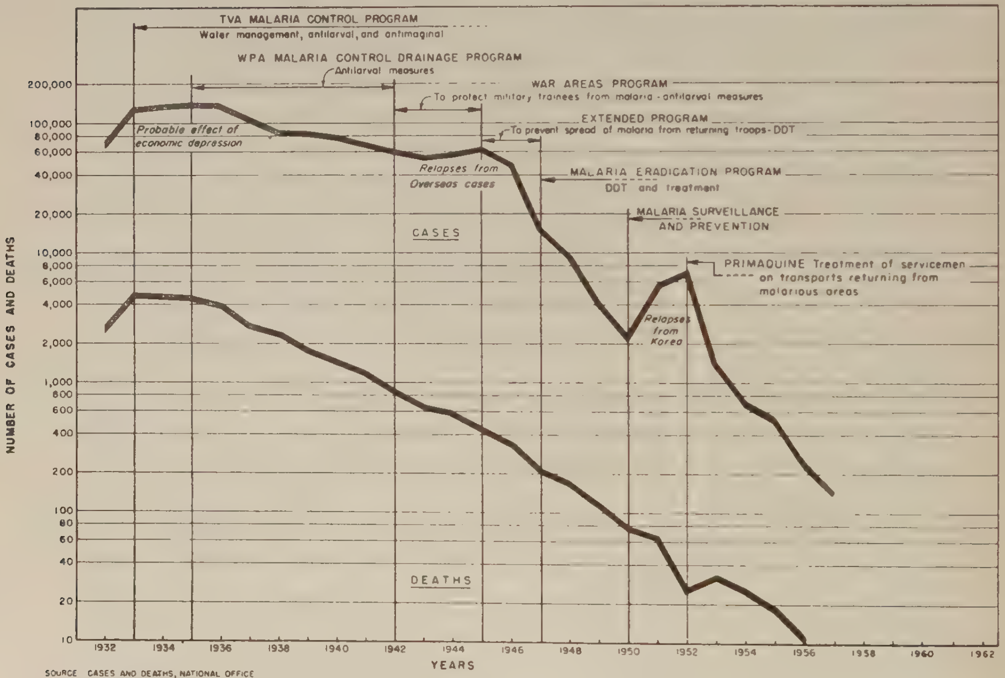
In addition to the events noted in figure 1, other changes occurred more or less simultaneously which almost certainly contributed to the reduction in malaria. These were first summarized in 1948 (23), but their antimalaria impact has continued and presumably has been amplified during the intervening decade. They include economic improvement in malarious as well as non-malarious areas; more effective diagnosis and treatment of the disease; population movements in traditionally endemic States out of rural environs in which malaria could be transmitted, to urban situations where it could not; the increasing domestic use of insecticides and insect-proofing against mosquitoes, houseflies, and other annoying insects; and the deviation of *Anopheles quadrima-*

culatus from man to cattle in many rural sections of the southeastern States where cattle raising has become increasingly important in the local economy.

Actual mortality and morbidity from malaria no longer occur in most of the areas in this country where previously they were of devastating importance. They cannot occur elsewhere at more than very low levels, if at all, according to the data shown in figure 1 and table 1.

Figure 1

REPORTED MALARIA MORBIDITY AND MORTALITY
IN THE
UNITED STATES
1932–1957



SOURCE CASES AND DEATHS, NATIONAL OFFICE OF VITAL STATISTICS

ATLANTA GA FEB 1958
58 245 REV AUG. '58

As a matter of fact, the steadily decreasing numbers of deaths certified year after year as «due to malaria» are rarely verifiable, and the vast majority yof the parasite-positive cases are service men, veterans, travellers, or imported laborers either with histories of malaria or with

TABLE 1 — *Reported malaria mortality, morbidity, and cases appraised in the United States, 1948-1957*

Year	Reported eaths from malaria [1]		Reported cases of malaria [1]		Reported malaria cases appraised [2]			
	Number	Rate/ /100,000	Number	Rate/ /100,000	Total	Confirmed [3]	Presumptive [4]	Primary indigenous [5] (confirmed or presumptive)
1948	170	0.1	9606	6.6	770	242	Undetermined	Undetermined
1949	118	0.1	4151	2.8	514	60	46	63
1950	76	0.1	2184	1.4	713	30	39	45
1951	64	0.0[6]	5600	3.7	1874	1272	5	19
1952	25	0.0[6]	7023	4.5	3098	2707	16	50
1953	32	0.0[6]	1310	0.83	449	217	3	33
1954	24	0.0[6]	715	0.44	130	97	5	13
1955	18	0.0[6]	522	0.32	472	47	388	18
1956	11	0.0[6]	234[7]	0.14	194	93	32	10
1957	—	—	132[8]	0.08	138	97	6	11

exposures to malaria outside of this country. It must be admitted, however, that a very small percentage of the confirmed cases do occur in persons who have never been abroad. How, then, are we to know whether or not malaria has been extinguished from the United States, or from any considerable part of it? As observed by the WHO Expert Committee on Malaria (18), the «recognition of absolute freedom from transmission, or of absolute absence of remaining infections, presents insuperable obstacles».

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[1] Source: Cases and Deaths, National Office of Vital Statistics; Appraisal data from the Communicable Disease Center, U. S. Public Health Service.

[2] By State, local, or Communicable Disease Center epidemiologists.

[3] Parasites found in blood smear.

[4] Clinically and epidemiologically consistent with malaria, but parasites not found in blood smear.

[5] Initial attacks resulting from infection acquired within a specified area (U. S. A. in this table). The lack of agreement of case numbers in Table 1 with those in references mentioned in the text for the same years is due to the inclusion of additional data which have become available since the original tables were published.

[6] Less than 0.1/100,000.

[7] 238 cases reported to the Surveillance Section, Communicable Disease Center, U. S. P. H. S., for the same year.

[8] 157 cases reported to the Surveillance Section, Communicable Disease Center, U. S. P. H. S., for the same year.

As indicated above, efforts have been made since 1947 to appraise reported malaria cases and deaths. The original objectives were to stimulate more accurate and complete reporting of these events and to identify residual malaria foci. Since 1951, an additional goal has been to ascertain when and where the criteria of malaria eradication have been fulfilled. These activities have involved many persons with varying interests, motivations and competences with respect to malariology within a very large country containing numerous relatively independent health jurisdictions. The assumption of even gross consistency in procedures and conclusions under these conditions would be naive were it not for the fact that these investigations, made by State, local, and Federal health personnel, have been coordinated and followed up since the beginning by the Communicable Disease Center, final decisions as to case categorization being made in the State health departments concerned. Thus the positive findings probably have high degrees of verity and consistency; negative ones are obviusly less dependable.

In 1947, the special mission of the Communicable Disease Center medical and nurse epidemiologists, working êith their State counterparts, was to study the diagnostic and reporting practices of physicians in malarious areas (*24*). It was quickly ascertained that both over-reporting and under-reporting, more frequently the former, occurred in many places. Relatively few practicing physicians, especially the older ones, made any effort to verify their clinical impressions with laboratory evidence. On the one hand, any fever of uncertain origin or almost any other ill-defined clinical complaint was usually reported as malaria, especially if it disappeared after antimalarial treatment; on the other hand, certain of the practitioners felt that malaria, verified or not, was too common and unimportant to be called to official attention. In some States, it appeared that disease-notification systems which did not identify or locate patients led to unintentionally spurious case reporting. Certifications of death due to malaria were most commonly justified on the inferential basis of unconfirmed histories of malaria in the individual or even in his family.

In all instances, the Communicable Disease Center personnel tried to be helpful to the physicians individually and collectively by demonstrating the ease of obtaining laboratory evidence to confirm or query tentative diagnoses of malaria, and to provide leads relative to non-malarial diagnostic problems. Refresher discussions were held with local medical societies on the parasitology, pathology and epidemiology of malaria, and information concerning newer methods of treatment was presented.

In 1948, attention was directed more specifically to the appraisal of individual cases (25), and it became evident that a standard categorization of these was desirable. After some trial and experimentation with more complicated systems, the term «positive», later replaced (in 1949) by «confirmed», was used to indicate those cases in which malaria parasites were found in blood smears by laboratories approved by their State health departments. The word «presumptive» was applied to cases clinically and epidemiologically suggestive of and compatible with malaria, but in which parasites were not found. Special efforts were made to determine where and when the infection was probably acquired, to identify those which were indigenous from those contracted outside the continental United States. In general, the assumption was made that if the confirmed case was a serviceman or veteran with recent overseas duty in malarious areas, his infection was more likely to have originated outside the United States. The same was assumed to be true of civilian cases who had travelled recently in endemic areas in other countries. The term «primary indigenous» was reserved for application to those confirmed cases who had never been out of the United States and who were not known to have experienced a prior malaria attack, though this last could not always be determined with certainty.

Table 1 shows these findings. The increased numbers of reported cases, appraisals,, and confirmations in 1951 and 1952 and, to a lesser extent in 1953, are due largely to malaria occurring in the repatriated veterans of the Korean episode. These were augmented during 1952 and 1953 by 33 confirmed and two presumptive cases among Girl Scout campers, staff members, and local residents at Lake Vera, California; the outbreak was shown to be due, presumptively, to an infected Korean veteran who slept outdoors near the Camp early in July (26). While there, he experienced an acute relapse of confirmed vivax malaria. Anopheline mosquitoes of infectible species were found to be numerous in the Lake area. Cases of malaria made their appearance beginning in late July among girls who had left the camp and returned to their homes in diverse areas. Nine cases appeared in 1952 and six of these relapsed in 1953; twenty-four more persons experienced their first symptoms in 1953. Antilarval control measures effected early in 1953 were apparently successful as no new cases had been reported by the end of January, 1954 (27).

Another and more recent incident, directing attention to an entirely different concern of the malaria eradicator, is recorded this year by the Communicable Disease Center (28). Of 21 primary indigenous cases of malaria reported throughout the country during 1956 and 1957 (table 1), six occurred in Cherokee Country, Oklahoma, the seat of the Cherokee Indian Nation. This unusual number of cases in a small area prompted an investigation. It revealed that the cases, all of whom were Indian children (two never out of the County), were parasite positive (blood smears had been saved), and that each had yielded dramatically to chloroquine-primaquine treatment. Two more highly presumptive cases were found during the investigation. Sloughs and streams were numerous in the area, and mosquitoes were said to be abundant in the summertime. Housing was primitive. No programmed house spraying had been conducted in the specific area which was admitted by local health authorities to be historically malarious, a few cases from this area being reported and confirmed each year. Proprietary antimalarials, which have disappeared from most erstwhile endemic areaes, were available in local stores. No evidence of imported malaria could be adduced, and it was concluded that the focus was one of surviving endemicity. It has since been throughly treated with insecticidal sprays.

In 1957 (29), six primary indigenous cases occurred in California. Four of these were American workers on a farm located a quarter-mile from a Mexican labor camp. *Anopheles freeborni* was numerous in the area when the cases occurred. None of the four American cases are known to have travelled out of the region. The other two cases from different counties also were without history of recent travel. It seems highly probable that all of these were newly transmiteed from Mexican laborers. Three more apparently unrelated cases have been reported from this same County in 1958; the State and local health authorities are working vigorously to nullify these possible sources of new infection.

Malaria appears to be acquired abroad by American civilians as readily as by soldiers. In 1956, of 194 appraised cases, 46 occurred in military personnel, and 57 in civilians who had travelled in Mexico or in one or several of 24 other countries where the possibility of exposure to malaria could not be excluded (29). In 1957, of the 138 appraisals, 56 were persons with military experience overseas, 15 were civilians who had been in Mexico recently, and 22 were civilians who had been in 21 extraterritorial areas where malaria is presumed to be endemic (29).

Almost every year since malaria surveillance activities were started, there have been one or a few confirmed, primary indigenous cases which appeared to be sporadic as far as relation to other known cases in time and space is concerned. No likely explanation — such as relapse; transfusion; experimental, therapeutic, or accidental (drug addiction) inoculation; travel abroad; or transmission from imported sources — could be uncovered. Admittedly remote possibilities may be that they are not, in fact, primary attacks but delayed relapses from forgotten or unknown infections during childhood or from exposures abroad not remembered or admitted — or they may be solitary recipients of recent transmission from an undiscovered, imported gametocyte carrier.

These incidents clearly indicate that practically all theoretically possible mishaps which can lead to the survival or re-establishment of malaria do occur during and after eradication programs. While the instances alluded to are the only ones of which we are aware, it is quite possible in our huge terrain potentially receptive to paludism that others have transpired and either have died out unnoted or continue to exist undiscovered or unreported thus far. Again, lack of evidence or negative evidence is not as trustworthy as positive findings.

It is clear from the foregoing that, in spite of what we believe to be a reasonably successful approach to the eradication of indigenous malaria in the United States, there are areas within it which could not now qualify for total eradication status under present criteria. The socio-economic forces which militate against its final and complete accomplishment will most certainly continue in this country, as they will in all others, until malaria endemicity nears the vanishing point in the rest of the world.

This status, namely that of freedom from native malaria with the current expectation of introduced malaria, against which constant surveillance and reprisal mechanisms must be maintained, is referred to by our appraisal specialists in the Communicable Disease Center as «effective» rather than «total» eradication (29). I prefer the term «eradication of indigenous or endemic malaria» rather than «effective eradication» as being more truly indicative of the situation. It is the opinion of these authorities that «assuming continuing maitenance of averseas military installations and continuing widespread international travel by U. S. nationals». we should anticipate «forty or fifty cases per year through the early 1960's» (29). To these two major avenues of malaria importation might well be added that of migrant laborers entering the United States each year in increasing numbers from areas abroad in which indigenous malaria has not been eradicated.

While we await the day of the eradication of endemic malaria in the rest of the world, all of our State, local, and Federal health personnel concerned should make every effort to hold and expand the gains which have been achieved against malaria to safeguard the tremendous investment already made (1) toward its eradication, and to exploit to the utmost every new technical advantage that research on basic as well as applied aspects of insecticidal technology or mass chemotherapy can contribute — and our laboratories and other research facilities where such investigations can be pursued should vie aggressively with each other to produce more practicable and effective antimalarial procedures than we now possess.

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MALARIA ERADICATION PROGRESS IN GREECE

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Experience gained recently in Greece has contributed to the shaping of the eradication strategy (28-31, 33). It may then be interesting to review our post-war anti-malaria work in the light of this new concept and assess its progress towards eradication.

As is known (19), an eradication programme comprises four phases: preparatory, attack, consolidation and maintenance.

Data collected in the pre-D. D. T. era by Greek workers and their colleagues of the Greece Mission of the Rockefeller Foundation (18, 3-9, 32, 34, 35, 26, 27, 24) fulfilled adequately the requirements of the preparatory phase.

The extensive 1946-1950 insecticidal campaign, in which more than 5,000 villages were residually sprayed yearly (23, 11, 14), would correspond to the attack phase[1]. But some of the requirements of an eradication programme were of necessity missing. Among other things, the unsettled conditions in 1948-1949 did not permit as thorough an insecticidal coverage as it should have been. Moreover, neither passive nor active case detection existed then. The evaluation of results was based on malariometric rates (23, 11, 14) and malaria mortality in towns (10, 11, 14). Both these sets of data showed a hundredfold decrease in five years[2]. This was exceedingly good for ordinary malaria control. But if eradication had been the aim, were the conditions right for ending then and there the attack phase?

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[1] Detailed numerical data appear in Table 1.

[2] Detailed numerical data appear in Table 2.

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TABLE I_SUMMARY OF POST-WAR ANTI-MALARIA ACTIVITIES IN GREECE, 1946-1958

Periode	YEAR	HOUSE - SPRAYING		GROUND LARVICIDING		EPIDEMIOLOGICAL SURVEILLANCE (ACTIVE CASE DETECTION)				ANTI-RECIDIVE TREATMENT (Positives Treated)
		VILLAGES SPRAYED	POPULATION	TOWNS PROTECTED	POPULATION	VILLAGES AND TOWNS SURVEYED	POPULATION	VISITS MADE	BLOOD SMEARS TAKEN	
	PRE-WAR	—	—	73[a]	900.000[a]	—	—	—	—	—
I	1946	4,139	2, 852, 367	147	1, 582,000	—	—	—	—	—
	1947	5, 821	3, 514, 335	115	1, 383,000	—	—	—	—	—
	1948	4. 798	3, 530. 024	92	1. 241. 226	—	—	—	—	—
	1949	5, 440	4, 008. 029	118	1. 569. 300	—	—	—	—	—
	1950	5, 137	3, 198. 937	93	1. 445. 685	—	—	—	—	—
II	1951	1, 961	1, 303, 866	122	1, 520. 316	861[b]	549. 552	7. 003	951	—
	1952	401	278. 497	79	1, 503, 256	2,746	2. 258, 451	28, 231	7. 609	—
	1953	615	459, 348	101	1. 625, 955	2, 638	2. 935. 972	18. 365	10, 752	—
III	1954	2. 003	1, 335, 344	120	1. 694. 802	3, 116	2. 914. 964	24, 630	16, 662	—
	1955	2, 039	1, 337, 976	144	1, 823, 432	3, 381	4, 049. 043	25. 921	17, 673	—
	1956	1, 225	876, 861	143	1, 819, 000	3, 435	4, 144. 143	31, 073	14, 683	—
IV	1957	1, 327	948, 409	76	1, 555, 104	3, 894	4, 285, 513	32, 108	29, 067	4.071
	1958[c]	570	—	53	—	4, 586	—	—	—	1, 468

REMARKS:

a, Data for 1999. ——— b. Peloponnese and Crete only.—c. Planned work

I

TABLE II_SUMMARY OF MALARIA MEASUREMENTS, GREECE 1946–1957

Periods	YEAR	MEAN PARASITE RATES[a]		SPECIFIC MALARIA MORTALITY IN TOWNS[b]	Nº OF DEATHS NOTIFIED	LABORATORY CONFIRMED CASES[c]
		SCHOOL %	INFANT %			
	PRE-WAR	17.23[d]	10.0[d]	31.25[e]	4.804[f]	960.800[g]
I	1946	1.76	0.29	—	—	—
	1947	0.21	0	—	—	—
	1948	0.21	0.35	—	—	—
	1949	0.15	0.38	1.35	—	—
	1950	0.16	0.42	0.53	—	—
II	1951	0.03	0.04	0.28	—	43[h]
	1952	0.03	0.05	0.12	—	408
	1953	0.04	0.10	0.06	—	1,403
III	1954	0.09	0.11	0.07	—	2,350
	1955	0.12	0.13	—[i]	18[j]	1,642
	1956	0.02	0	—	10	683
IV	1957	0.015	0	—	12	1,468
	1958[k]	—	—	—	—	—

REMARKS:

a Respectively 200 and 100 towns and villages surveyed yearly.
b. Per 100.000 inhabitants.
c. Through active detection.
d. 1933-39 average
e. 1930-39 average
f. 1930-39 average
g. Estimated 1930-39 average
h. Peloponnese and Crete; another 144 positives were detected passively in the remaining Regions
i. Data discontinued
j. No data available before 1955
k Planned work

II

At any rate, the scarcity of insecticides in the world market prompted a drastic reduction of residual house-spraying to 1/10th its previous scale of application in the following 3 years. At the same time a programme of active case detection and therapy, or epidemiological surveillance, was instituted (14). As expected, it took the whole of this period before we could get an accurate enough picture of the malaria situation. It was thus found that, although some of the 50 Districts of Greece were practically malaria-free, quite numerous (though generally small) foci persisted through the remaining country (14). *P. falciparum* infections represented in 1951 20 % to 25 % of all positives detected. The appearance of anopheline resistance coincided with this period (11--13, 20-22, 25), and before we could devise ways and secure means to counteract it (11, 12-14), it did interfere with the efficiency of the rather rudimentary house-spraying programme of that period (12).

If this 1951-1953 period could be said to correspond to a premature consolidation phase, the next one, covering the years 1954-1956, would be a secondary attack phase, at least a partial one. Insecticides were by then plentiful and their use was extended to about 2,000 villages yearly (14). Because of resistance, B. H. C., chlordan, dieldrin, as well as D. D. T., were used in alternation and, frequently, the spraying had to be repeated once or even twice in the year (11, 12-14).

Throughout the second and third periods malariometric rates, despite a relative rise in 1952-1955, did not reach the previous levels, dropping in 1956 to 1/850th their pre-war values (14, 1). Malaria mortality in towns was decreasing steadily (14, 15). The positive cases detected by epidemiological surveillance, actively as well as passively, reached a maximum in 1954, with 2,350 cases (14). Anopheline resistance in the adult stage, though still polyvalent and wide-spread, did not seem, on the whole, to have increased beyond the levels reached in 1953 and was quite manageable through the measures taken (15). But, on the other hand, we found out in 1956 that in E. Peloponnese the larval stages of *A. sacharovi* had become resistant to the I group of chlorinated insecticides (17).

Beginning 1957, the situation had improved sufficiently so as to permit a re-orientation of the programme towards eradication (15). Here are some of the measures taken in this connection (16):

Fifty malaria inspectors were added to those serving with our Directorate, bringing their total to 250. Refresher courses were given to all the technical personnel Twelve Field Parasitological Laboratories were added to the 8 existing and 3 Experimental Malaria Stations were established. The recently created 1,048 Rural Dispensaries, with their 1,081 physicians, 306 midwives and 223 nurses were involved in our epidemiological surveillance.

From the technical point of view we inaugurated in 1957 what we call the anti-recidive treatment: In 972 villages and towns, primaquine was given daily for 14 days by our technical personnel, during the pre-epidemic season, directly to the mouth of the positives detected in the previous three-year period. A total 4,071 individuals received a full treatment, i. e. 93.7 % of the group; 8,163 smears taken during the subsequent 6 months showed a 3 to 5 % relapse rate (16).

The epidemiological surveillance improved both qualitatively and quantitatively, as shown by the figure of smears taken, which more than doubled. As for treatment itself, it may be noted that all suspect cases receive single-dose pyrimethamine; single-dose chloroquine is added in case of fever. After eventual laboratory confirmation we use primaquine, preceded by chloroquine if there is still fever.

In that same year (1957) 1,327 villages were residually sprayed, mostly with D. D. T. and B. H. C., not to mention the auxiliary methods such as ground-larviciding in selected urban areas, drainage, Gambusia stocking in rice-fields and swamps, limited chemoprophylaxis with pyrimethamine, etc.

By the end of 1957 the residual endemicity was much more localized than ever before. Most of the 420 villages and towns, found positive in that year, belonged to 9 important geographical areas[1] Autochtonous cases had disappeared not only from Crete, but from mainland regions, such as Epirus, known not so long ago for their hyperendemic malaria. All of the 1,468 infections detected in 1957 were due to *P. vivax* except 5 which were due to *P. malariae*. Even assuming that for every 2 cases detected 3 others had escaped detection, we are very far indeed from the million infections occuring yearly before D. D. T. Twelve deaths were reported as due to malaria (which seems excessive) as against 4,800 annual deaths in the pre-D. D. T. period. The population protected reached 4,285,881 at a cost of U. S. $ 800,000, all from Government sources. This outlet represents but 1/60th of the losses

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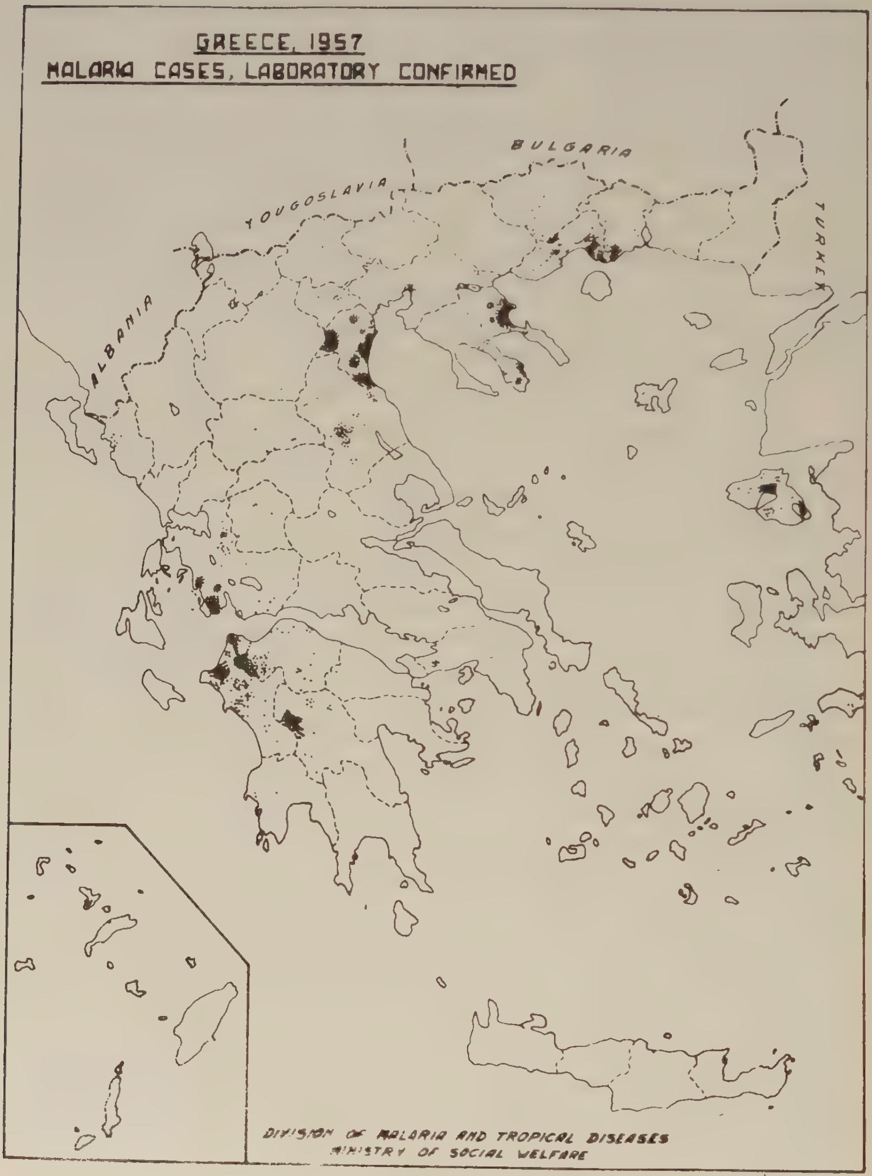
[1] See Map.


GREECE, 1957
MALARIA CASES, LABORATORY CONFIRMED
BULGARIA
YOUGOSLAVIA
ALBANIA
TURKEY
DIVISION OF MALARIA AND TROPICAL DISEASES
MINISTRY OF SOCIAL WELFARE

III

caused by malaria 15 years ago. At the same time other insect-borne diseases, so prevalent in the pre-D. D. T. era, have practically been wiped out (16) and, as expected (2), lethality from some infectious diseases, such as pneumonia etc., was further reduced. Nuisance from many domestic pests has ceased (15, 22). And, without the menace of malaria, rice production increased by a factor of 15.

Additional steps are being taken so as to further improve the efficiency of the 1958 programme (16). Blood examination for malaria parasites in all in-patients and the febrile out-patients became recently compulsory in the 149 State-dependant Hospitals and facultative in the 350 private Clinics[2]. We pursue our efforts to secure an even closer cooperation with the Health Institutions and Establishments of all other governmental and semi-autonomous Agencies, as well as with the 5,600 general practitioners. We are also attempting to form local Voluntary Malaria Eradication Groups in villages where neither Dispensaries, nor physicians operate. And Health Education is not neglected.

Anti-recidive treatment has already been given in March to the positives detected in 1957. Insecticidal operations in 1958 will be limited mostly to the 9 areas with important residual malaria. They are expected to come to an end next year or, at the latest, in 1960. And it is hoped that the maintenance phase will be reached by 1963 or 1964. By then the secular scourge of Greece, so thoroughly described by Hippocrates, may well be a thing of the past.

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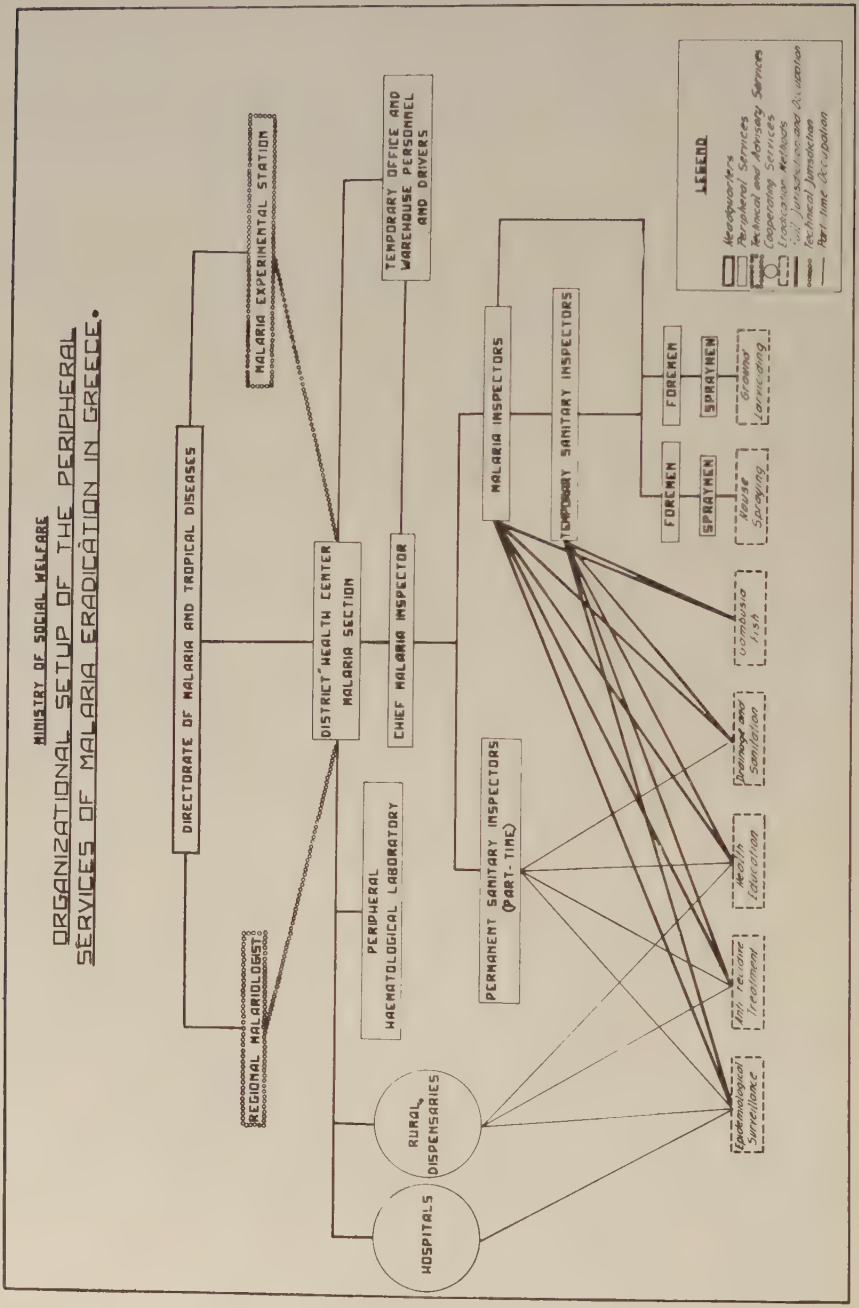
[2] The present Organizational Setup of the Peripheral Services of our Directorate appears in the appendend Graph.


MINISTRY OF SOCIAL WELFARE

ORGANIZATIONAL SETUP OF THE PERIPHERAL SERVICES OF MALARIA ERADICATION IN GREECE.

DIRECTORATE OF MALARIA AND TROPICAL DISEASES
MALARIA EXPERIMENTAL STATION
REGIONAL MALARIOLOGIST
DISTRICT "HEALTH CENTER MALARIA SECTION
TEMPORARY OFFICE AND WAREHOUSE PERSONNEL AND DRIVERS
CHIEF MALARIA INSPECTOR
PERIPHERAL HAEMATOLOGICAL LABORATORY
MALARIA INSPECTORS
TEMPORARY SANITARY INSPECTORS
PERMANENT SANITARY INSPECTORS (PART-TIME)
FOREMEN
FOREMEN
SPRAYMEN
SPRAYMEN
House Spraying
Ground Larviciding
Gambusia fish
Drainage and Sanitation
Health Education
Anti relapse Treatment
Epidemiological Surveillance
RURAL DISPENSARIES
HOSPITALS
LEGEND
Headquarters
Peripheral Services
Technical and Advisory Services
Cooperating Services
Eradication Methods
Full Jurisdiction and Occupation
Technical Jurisdiction
Part time Occupation

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BREVE NOTE SUR L'ETAT DE L'ERADICATION DU PALUDISME AU PORTUGAL (CONTINENTAL)

AMADEU LOBO DA COSTA

Un plan d'éradication du paludisme visant les régions paludiques du Pays, étant conçu aux plans préconisés par les plus avisés experts de l'O. M. S., ne serait pas très différent, du point de vue technique, des luttes de simple contrôle qu'il y a déjà quelques années on fait chez-nous.

Les différences entre les deux méthodes de prophylaxie sont seulement de quantité, et visent surtout à l'étendue et profondeur de l'application des mêmes procès techniques de lutte; la même lutte anti-imago, parfois renforcée avec des pratiques anti-larvaires, égal traitement radical des cas, la même détection des porteurs, similaires préocupations avec l'assistance médico-sociale des groupes migratoires de la population exposée.

Pour cela la méthode de contrôle, quand il est correctement exécuté, nous mène, à la fin d'un certain temps, à l'éradication du parasite et de la maladie, avec la même certitude et confiance des plus ambitieux plans d'éradication.

C'est, par exemple, ce qu'on a vérifié en Italie et, semblablement, chez-nous dans certaines zones impaludées situées au nord du Tejo et dont sa défense anti-paludique est confiée aux stations et postes de Azambuja, Montemor-o-Velho, Pocinho et Mirandela, des Services d'Hygiène Rurale et Défense Anti-Paludique.

Ainsi, dans notre Pays, dans lequel la morbidité a décrû en 1955, de 50 000 cas annuels pour 168, et où nous ne signalons que la persistence d'une seule espèce de vecteur en de petits foyers de faible transmission, l'exécution d'un plan d'éradication n'apportait pas la solution d'aucun problème technique spécial, parce qu'il se mélangeait avec la réalisation d'un autre plan de lutte anti-paludique tout à fait semblable à celui des années antérieures.

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Par le calcul ci-joint on peut voir que les résultats prévisés pour les années à venir, si nous avions continué à faire les simples luttes de control, seraient pareils à ceux qu'on prétendait obtenir par l'exécution d'un plan d'éradication.

Mais en exécutant notre plan d'éradication, nous voulions atteindre, à la fin de 3 ou 4 années, «le point zéro» de la morbidité; ceci, avec les luttes de contrôle, nous prendrait beaucoup plus de temps avec tout ses inconvénients.

Les résultats obtenus dans les dernières années sont:

Années	Primo-infections
1950	4 664
1951	2 141
1952	1 216
1953	534
1954	368
1955	168

Ce que nous a permis de prévoir:

1956	70 à 80
1957	30 à 40
1958	10 à 20
1959	moins de 10, ce que dans la pratique

ce doit considérer comme à l'éradication.

Il faut remarquer que le numéro de cas vérifiés en 1954 s'éloigne un peu de ce que le calcul ferait prévoir. C'est à cause des difficultés financières que le control n'a pas été fait, cette année, en des conditions normales dans une certaine zone de la vallée du Sado, et, pour cela, on a vérifié une incidence un peu anormale.

Ayant commencé un peu tardivement, par des questions d'ordre administrative, à mettre en exécution en 1956 le plan d'éradication, soit disant, à faire une lutte contre le mostique vecteur, ayant pour base l'application des insecticides d'action persistante couvrant la totalité des regions où il y avait encore la transmition, on a vérifié les résultats suivants:

Années	Primo-infections
1956	89
1957	24
1958	jusqu'à la fin du mois de Juillet seulement 3.

Au même temps nous avons fait la détection du paludisme entre la population exposée, fixe ou migratoire.

À tous les médecins du Pays ont été distribués des carnets d'avis télégraphiques avec lesquels, et gratuitement, ils communiquent à nos services le simple soupçon d'un cas de paludisme, ce qui nous permet une action rapide.

À propos on remarque qu'avec cette mesure, en plus de bénéficier nos procès de détection, nous croyons pouvoir limiter certaines anomalies vérifiées dans la notification des cas de maladie et de mort par le paludisme, publiés dans l'*Annuaire Démographique*. Celui-ci vient enregistrant, d'après 1931, le numéro de décès par paludisme passif des plus grands doutes et réserves, parce que la plupart des diagnostics on été faits «post-mortem», se fondant, dans la meilleure des hypothèses, en des informations cueillies localement par le médecin.

Vraiment, ils seront très rares les cas de paludisme qui, étant traités et suivis par un médecin, finissent, encore aujourd'hui, par la mort du malade.

Le plus fréquent c'est que le médecin, qui vérifie le décès, n'a pas été l'assistant, pendant la maladie, faisant ainsi un dignostic de valeur scientifique moins que nul. À cause de cela, on ne peut pas s'étonner que, parmi les cas de mort qu'on a attribué, dans ces dernières années, au paludisme et que les Services d'Hygiène Rurale et Défense Anti--Paludique on pu étudier ultérieurement, pas un a présenté des difficultés d'interprétation. Au contraire il a été toujours facile nier de tels diagnostics, avec la certitude absolute, parfois même avec l'accord du médecin qui avait fait la déclaration...

Les erreurs se sont vérifiées toujours, comme nous avons déjà dit, mais elles ont pris dernièrement une plus grande importance due à la petitesse des numéros en présence. Si, cependant, nous acceptions les numéros publiés par l'*Annuaire Démographique* comme étant passablement exacts, nous serions conduits au paradoxe suivant:

Dans la Métropole:

Années	Cas	Décès	Léthalité
1954	483	14	2,9 %
1955	246	7	2,8 %

Dans notre province de Mozambique:

Années	Cas	Décès	Léthalité
1951	93 748	34	0,03 %

C'est à dire, malgré les progrès de la moderne quimiotérapie, on aurait vérifié, à la Métropole, avec la prédominance du *P. vivax*, une léthalité d'à peu près 3 %.

Cependant, à Mozambique, en 1951, où grasse un paludisme beaucoup plus grave avec l'empire du *P. falciparum* parmi 93 748 cas notifiés, sont morts seulement 34 individus; par conséquence, on a vérifié dans cette province une léthalité de 0,03 %, soit à peu près plus de 100 fois plus favorable!

Dans nos Services d'Hygiène Rurale et Défense Anti-Paludique, depuis 1946, qu'on n'enregistre pas un seul cas de mort par paludisme.

Mais continuons notre exposition.

L'efficacité des plans de combat au paludisme dépend, pour la plupart, de l'étendue du territoire, bénéficié par ces plans. Ainsi, un plan d'éradication du paludisme, au Portugal, difficilment pourrait être mis en équation dans l'ignorance de la frontière terrestre qui nous sépare des régions paludiques espagnoles.

Si les méthodes furent diverses, ici et là, si les efforts ne sont pas synchroniquement conduits, tout l'espoir de succès se pourra, certainement, perdre.

Ce problème prenait pour nous plus d'acuité et d'importance dans la «Region Paludique Continentale du Sud» (Cambournac), parce que c'est là que, de l'un et de l'autre côté de la frontière, prévalait encore des petits foyers de paludisme endémique, de quelque importance.

Nous n'ignorions pas que les Services Anti-Paludiques espagnols avaient été très actifs dans les dernières années, et on peut même assurer que ses disponibilités financières et la compétence téchnique de son personnel, leurs avaient permis réaliser des luttes anti-imago beaucoup plus vastes que celles que nous mêmes avions réussi à obtenir jusqu'ici.

Cette circonstance, cependant, quoique très favorable, ne pouvait pas modifier entièrement notre point de vue. Bien au contraire, nous devions même accentuer qu'un «plan d'éradication du paludisme», en Portugal ou en Espagne, malgré les bas valeurs paludimètriques observés en cette occasion, ne pourrait pas être couronné de succès, s'il se bornait seulement aux limites géopolitiques de ces pays.

Dans ce sens se sont prononcés les services spécialisés de l'O. M. S. en plusieurs cas analogues.

Du même avis étaient nos ilustres confrères espagnols, et ainsi on a conclu un accord espagno-portugais pour l'éradication du paludisme à être mis en action dans la Péninsule par les deux services nationaux responsables, en collaboration, et que nous attendons pouvoir mettre en exécution prochainement.

De la même façon nous ne pouvions pas laisser de faire attention à de certains éléments de perturbation, étranges, résultant de l'intensité des relations avec d'autres continents où le paludisme grasse encore sous la forme endémique.

Les fréquentes rélations que nous entretenons avec nos provinces d'outre-mer, permettant l'entrée de qualques porteurs de parasites, pourrait être la cause de très graves épidémies du paludisme. Celles-là sont d'autant plus à craindre, que l'éradication de cette maladie, pratiquement déjà obtenue, aura conduit à la parte de l'immunité collective.

Les services responsables ont besoin de faire la détection de tous les immigrants suspects, pour préserver les bénéfices de l'éradication.

Pour cela, nous avons demandé la collaboration de la Police Internationale et de la Défense de l'État, que, dû à ses fonctions, nous peut mettre rapidement en contact avec les immigrants.

Pour finir nous dirons que dans les zones où la transmition est brisée, et par conséquence les pulverisations sont finies, nous cherchons activement les cas de paludisme, et nous pouvons dire que dans les milliers d'individus observés jusqu'à présent nous n'avons pas trouvé un seul cas de paludisme.

PEUT-ON ENVISAGER L'ERADICATION DU PALUDISME DANS LA REGION FORESTIERE DU SUD CAMEROUN?

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La possibilité de l'éradication du Paludisme en Afrique Tropicale est l'objet de nombreuses controverses. Les observations recueillies au cours des travaux (recherches, enquêtes, campagnes d'aspersion) effectués ces dernières années dans la région forestière du Cameroun méridional et spécialement dans la Zone Pilote d'Expérimentation Antipalustre de Yaoundé, pourraient aporter à cette question une réponse satisfaisante, tout au moins en ce qui concerne la région intéressée.

A cette fin, nous décrirons d'abord quelles étaient initialement les conditions malariologiques de la contrée: milieu, vecteurs, transmission, endémicité. Nous exposerons ensuite nos travaux de lutte antipaludique, et leur retentissement, tant sur l'état sanitaire de la population, que sur le devenir des Anophèles vecteurs.

PREMIÈRE PARTIE

LES FACTEURS DE L'ENDEMIE PALUSTRE DANS LA REGION FORESTIERE DU SUD CAMEROUN

Chapitre I

Le Milieu

Esquisse de Géographie physique et humaine

La région forestière du Sud Cameroun s'étend sur toute la largeur du Pays. Elle est limitée au Sud par les frontières de la Guinée Espag-

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nole et l'A. E. F., au Nord par une ligne Nkongsamba, Bafia, Nanga-Eboko, Batouri, un peu supérieur au 4ème parallèle, avec des prolongements au Nord sur le Mbam et la Haute Sanaga (Massif de Deng-Deng). Sa superficie est de 130 000 km² environ.

Cette région est constituée par un plateau précambrien d'une altitude moyenne de 800 mètres, qui descend par une série de falaises sur une plaine côtière d'une largeur inférieure à 100 km.

a. *Climat*

Le climat est équatorial tétraorique, avec deux saisons sèches (Décembre à Mars et Juin à Août) et deux saisons des pluies (le mois le plus humide est Octobre). Sur la plaine côtière, où ce régime est modifié par les moussons, il n'existe qu'une seule saison sèche, hivernale, et les plus fortes précipitations ont lieu en été.

La pluviométrie est forte sur la bande côtière (de 2 000 à 5 000 mm), moins élevée sur les plateaux (de 1 400 à 2 000 mm).

L'humidité relative est toujours élevée, avec une moyenne supérieure à 80 %.

La température moyenne se situe entre 24 et 26° C; les écarts sont faibles: 7 à 9° à Douala (minimum moyen du mois le plus frais: 22°; maximum moyen du mois le plus chaud: 32°), 8 à 12° à Yaoundé (minimum moyen du mois le plus frais: 19°; maximum moyen du mois le plus chaud: 30°).

b. *Phytogéographie*

Letouzey [(1958) (8)], dans son étude phytogéographique, distingue plusieurs types forestiers qui sont, d'Ouest en Est: la «mangrove» côtière à palétuviers; puis les forêts ombrophiles à feuilles persistantes sur la plaine côtière; sur le plateau, différentes formations semi-ombrophiles congolaises, partiellement caduques; dans la partie septentrionale et les prolongements Nord, la forêt semi-ombrophile à Sterculiacées. Cette dernière a été fortement attaquée par la hâche et les feux de brousse, aussi estelle souvent entrecoupée de petites savanes qui rendent très difficile sa délimitation. Au-delà, s'étend vers le Nord une région post-

-forestière, mosaïque de savane et d'ilôts de végétation arborescente, vestige de la forêt à Sterculiacées, qui fait transition avec les savanes guinéennes de l'Adamaoua.

Détruites par l'homme, les formations primaires sont devenues rares et la plus grande partie du massif est aujord'hui constituée par la forêt secondaire; celle-ci attaquée à son tour pour la création des plantations a fait place en maints endroits à des facies dégradés. Enfin, dernière création humaine, les cacaoyères constituent une formation végétale dont beaucoup de caractères écologiques sont forestiers.

En partant des pistes qui quadrillent la région, se rencontrent successivement: des plantations et des cacaoyères, puis les formations secondaires et enfin quelquefois un noyau de forêt primaire.

Le milieu forestier présente une grande constance d'humidité et de température. L'exubérance de la végétation s'oppose à la pénétration de la lumière et aux déplacements des insects, isolant chaque station écologique.

c. *Démographie et habitat*

Plus de 80 ethnies peuplent le Sud Cameroun, appartenant en majorité au groupe bantou; quelques-unes, dans l'Est, sont semibantoues: Makao, Kakas; enfin il existe moins de 10 000 Pygmées Babingas, nomades en voie de fixation rapide.

D'après les statistiques officielles et les cartes démographiques de Diziain [(1958) (3)], la population de la région forestière est de 1 200 000 habitants environ. Sa densité moyenne est de 9,2 h/km², mais sa répartition est très inégale: des densités de 90 h/km² sont enregistrées dans la Subdivision de Saa, de 20 à 30 h/km² aux environs de Yaoundé, de 5,5 h/k² dans le Ntem et de 0,7 h/km² seulement dans la région de la Boumba-Ngoko.

La majorité de la population est rurale et s'adonne à la culture du cacao et des plantes vivrières; dans l'Est, les cultures de maïs et de café sont étendues; en quelques points (Doumé,, Nanga-Eboko) on cultive le riz, mais cette activité est peu importante pour l'ensemble de la région. L'élevage se réduit aux chèvres, aux moutons et aux porcs, il n'y a pas de gros bétail.

Les villages s'allongent en deux rangées de maisons, le long des routes et des pistes qui forment un réseau carrossable bien développé. Pourtant, surtout dans le Sud et dans l'Est, des pistes ne sont encore accessibles qu'à pied, mais elles desservent une population généralement peu nombreuse. Inversement, dans les régions très peuplées, des villages se construisent sur des pistes secondaires encore inaccessibles aux automobiles.

La population est sédentaire; les cultures se trouvant près des villages, les habitants peuvent rentrer chez eux chaque soir; ajoutons que le climat ne se prête pas au sommeil en plein air, et que les activités nocturnes à l'extérieur (danses, réunions diverses) ne sont ici pas très fréquentes.

Exceptionnellement, sur des cultures éloignées des villages (rizières, champs de maïs), les villageois construisent des huttes provisoires où ils demeurent une partie de l'année. De même dans les estuaires et sur les rives des grands cours d'eau, existent des camps plus ou moins temporaires de pêcheurs [(Mouchet, 1958) (26)]. Enfin des Pygmées chasseurs nomadisent encore à travers la grande forêt. Ce sont là des exceptions qui n'intéressent que quelques dizaines de milliers de personnes.

CHAPITRE II

Les vecteurs

Biologie et importance respective des Anophèles vecteurs de la région Transmission du Paludisme

TRANSMISSION DU PALUDISME

La faune anophélienne du Cameroun méridional est connue par les travaux de Grunberg [(1905) (5)], Vaucel & Campourcy [(1943) (15)], Bernet [(1953 & 1954) (17, 18)], Rageau & Adam [(1953) (30)], Rageau, Adam & Rivola [(1953) (14)], Adam [(1955) (1)] et Languillon, Mouchet, Rivola & Rateau [(1956) (7)]. Ces auteurs ont signalé l'existence de quinze espèces d'Anophèles et mis en évidence le rôle vecteur de quatre d'entre elles: *A. gambiae, A. funestus, A. moucheti* et *A. nili*.

a) *Anophèles gambiae* — Giles 1902, est répandu avec une densité variable sur l'ensemble de l'aire forestière.

Ses gîtes larvaires exigeant un bon ensoleillement sont localisés dans les lieux déboisés, donc à proximité des agglomérations humaines; ils sont dûs la plupart du temps à l'activité de l'homme et les plus fréquents sont les flaques d'eau des routes et des pistes.

Ces biotopes ne sont en eau qu'en saison de pluies; le rythme annuel d' *A. gambiae* dépend donc étroitement des précipitations. De plus, l'eau des gîtes doit étre fréquemment renouvelée, ce qui n'a lieu qu'en pleine saison pluvieuse. Quand l'eau stagne et s'enrichit en matières organiques, les larves d'*A. gambiae* sont rapidement remplacées par celles de *Culex tigripes* [(Doby & Mouchet, 1957) (4)].

Les seuls habitats naturels où *A. gambiae* ait été rencontré sont les flaques d'eau laissées dans les creux de rochers en saison sèche, dans les rapides des fleuves (Ntem, Sanaga, Mbam).

Les imagos sont très anthropophiles, caractère accentué par l'absence de gros bétail et piquent très généralement à l'intérieur des maisons. Souvent les femelles n'y accomplissent pas la totalité de leur cycle gonotrophique, mais elles se reposent néanmoins sur les parois un temps suffisant pour avoir un contact efficace avec les insecticides muraux [(Mouchet & Gariou, 1957) (12)].

Tant par la localisation de ses gîtes larvaires, que par son comportement imaginal, *A. gambiae* peut presque, dans cette région, être considéré comme un insecte domestique et il est peu probable qu'il puisse se maintenir en dehors de contacts humains.

Les index sporozoïtiques que signalent les différents auteurs sont: 14,3 % à Yaoundé par Vaucel & Campourcy en 1943 (15), 17,6 % à Evodoula par Rageau, Adam &Rivola en 1953 (14), 5,3 % par Adam en 1956 dans la Zone Pilote (2), 8,6 % et 13,4 % dans la Zone Pilote, 10 % à Douala par Languillon, Mouchet, Rivola & Rateau en 1956 (7). La constance de la température et de l'humidité, la brièveté de la distance que l'imago doit parcourir entre les lieux de ponte et la longévité de cet insecte et expliquent en partie les index sporozoïtiques élevés.

Ces index prouvent qu'*A. gambiae* est ici un excellent vecteur et ils compensent en partie sa densité relativement faible en milieu rural; celle-ci, en effet, a été trouvée, en moyenne, inférieure ou égale à 1 anophèle par maison visitée, dans les villages de la région forestière.

A. gambiae n'a pénétré dans la forêt que dans la mesure où des destructions permettaient l'éclaircissement nécessaire aux gîtes larvaires; ce n'est certainement pas un insecte forestier et on peut le considérer comme surimposé dans ce milieu. Son adaptation ne semble d'ailleurs pas parfaite; à Biyan, (en Z. P., secteur C.), où des travaux de réfection de piste avaient détruit les gîtes classiques, on a vu, *A. gambiae* disparaître complètement de la localité, inapte qu'il était à coloniser d'autres gîtes. Cette adaptation, encore incomplète, pourrait expliquer les faibles densités observées en milieu rural.

Par contre, dans les villes et les localités de quelque importance, *A. gambiae,* en raison des conditions très favorables à la création de gîtes larvaires, offrait des densités plus élevés et était le vecteur dominant.

De ce fait, si *A. gambiae* n'était pas l'Anophèle le plus fréquemment rencontré dans les villages du Sud Cameroun avant les campagnes de désinsectisation, c'était par contre certainement lui qui se trouvait au contact de la masse la plus importante de population. A ce titre, il pouvait être considéré comme le vecteur numéro 1, avant le «house spraying».

b) Anophèles funestus — Giles 1900, a été signalé à Douala [(Bernet, 1953 et 1954) (17 &18)], à Yaoundé [(Vaucel & Campourcy) (15)], [(Rageau, 1949 & 1950) (28 & 29)], à Edéa [(Bernet, 1953) (17)], à Eséka et près des étangs artificiels d'Obili (Z. P. Secteur A) [(Adam, 1956) (2)].

Au cours de nombreuses prospections dans des villages réellement forestiers et non désinsectisés, du Sud et de l'Est, cette espèce n'a jamais été rencontrée. Cet Anophèle n'est donc pas non plus un mostique forestier; il n'a pénétré que dans des régions fortement dégradées par l'homme et surtout les grandes agglomérations.

Peu de choses sont connues sur ses gîtes larvaires au Sud Cameroun; ils ne semblent pas essentiellement différents de ceux qu'on observe en savane: grands marécages, bords des étangs et des cours d'eau dormants, etc....

Les imagos, d'après les auteurs précités, étaient très anthropophiles et entophiles. Leur densité était parfois élevée, comme Rageau l'a signalé pour Yaoundé. Les index sporozoïtiques rapportés sont de 10 % à Yaoundé [(Vaucel & Campourcy, 1943) (15)], 3,5 % en Z. P. [(Adam, 1956) (2)]. Ses possibilités vectrices sont donc bonnes, mais en raison de sa répartition réduite il ne peut être considéré que comme un vecteur secondaire.

c) *Anophèles moucheti* — Evans 1925, a été signalé au Cameroun par Zumpt en 1937 (16) et retrouvé par Adam à Mbalmayo en 1953 (1). Depuis, il a été capture dans de très nombreuses localités de la région forestière et de ses pourtours, [(Adam, 1956) (2)], [(Languillon, Mouchet, Rivola & Rateau, 1956) (7)]. Son aire de dispersion s'étend sur la plus grande partie du massif forestière contraficain.

Ses gîtes larvaires sont tous des gîtes naturels, bords herbeux et calmes des grands et moyens cours d'eau, souvent dans les nappes de *Pistia stratiodes*. Ils se trouvent aussi bien dans les lieux inhabités que près des villages. Le rythme annuel de cette espèce est lié au niveau des cours d'eau qui permet l'établissement des gîtes, mais la relation précise entre le régime d'un feluve et la pullulation du moustique est souvent difficile à établir avec précision.

Les imagos se rencontrent dans les habitations de la plupart des villages proches des cours d'eau où se développent les larves. Ils ont été trouvés dans 32 villages sur 86 prospectés dans l'Est et le Sud de la région forestière. Leur densité, généralement élevée, est en rapport avec la richesse et la proximité des gîtes larvaires (18 par habitation à Fegmimbang, Z. P. secteur C).

Dans les villages où il est présent, *A. moucheti* se montre anthropophile, entophage et entophile. Les femelles accomplissent la plus grande partie de leur cycle gonotrophique, qui dure de 48 à 72 heures, à l'intérieur des maisons [(Mouchet & Gariou, 1957) (13)].

Cependant, cet Anophèle peut très bien vivre en dehors de tout contact humain, se nourrissant sur la faune sauvage. Il est même probable que dans les stations habitées, une partie plus ou moins grande de la population d'*A. moucheti* continue à se nourrir sur d'autres hôtes que l'homme.

A. moucheti contrairement aux espèces précédentes, est un véritable insecte de la forêt, parfaitement bien adapté à ce milieu.

Les index sporozoïtiques rapportés sont de 1,4 % dans l'ensemble de la Z. P. [(Adam, 1956) (2)], 1,3 % à Ebogo et 8 % à Fegmimbang, Z. P. secteur C. [(Mouchet, 1956) (32)], [(Gariou, 1957) (20)]. Des dissections pratiquées sur des exemplaires capturés dans le Ntem, en petit nombre, il est vrai, ont fourni un I. S. supérieur à 15 % [(Languillon, Mouchet, Rivola & Rateau, 1956) (7)]. Les qualités vectrices de cet Anophèle sont aussi confirmées par la haute endémicité palustre qui régnait dans des villages où il était le seul Anophèle présent.

En fait, *A. moucheti* représente le véritable vecteur naturel du Paludisme dans la Forêt camerounaise.

d) *Anophèles nili* — Théobald 1904, est largement répandu en Afrique tropicale, aussi bien en savane qu'en forêt [(B. de Meillon, 1947) (9)].

Les prospections entomologiques dans le Sud Cameroun ont montré la présence de ses larves dans presque tous les cours d'eau. Par contre, les images n'ont été trouvés que dans un nombre restreint de localités: Z. P. [Adam, 1956) (2)], bords du Ntem et de la Kié [(Languillon, Mouchet, Rivola & Rateau, 1956) (2)], bords du Mungo (Mouchet, 1956). Dans ces villages il semblerait qu'*A. nili*, soit, au moins partiellement, anthropophile, entophage et entophile, mais les observations sont trop peu nombreuses pour donner sur son comportement des renseignements vraiment précis. De plus, la disproportion entre l'obiquité des gîtes lavaires et le petit nombre des localités où les imagos sont présents dans les maisons, peut laisser supposer de grandes variations biologiques, voire l'existence de différents biotypes.

Adam en 1956 (2) rapporte un index sporozoïtique de 2,8 % dans quelques localités de la Z. P.; dans le Ntem des index supérieurs ont été trouvés [(Languillon, Mouchet, Rivola & Rateau, 1956) (7)]. Cependant, du fait que cette espèce ne se rencontre pas très souvent dans les habitations, elle doit être considérée comme un vecteur secondaire.

TRANSMISSION DU PALUDISME

a) *Modalités générales de la transmission*

Nous avons vu dans les chapitres précédents qu'en règle générale la population passait la nuit entière dans ses habitations et que les vecteurs sont nettement entophages et entophiles. L'*infestation des vecteurs et la contamination humaine se font donc, dans la très grande majorité des cas, à l'intérieur des maisons*. De plus, les anophèles gorgés se reposent sur les murs.

On peut observer, en particulier, du fait des habitudes domestiques d'*A. gambiae*, de très petites chaînes épidémiologiques, presque familiales, intéressant une ou deux maisons proches de gîtes larvaires peu étendus, alors que le reste du village peut être indemne de vecteurs.

D'une façon générale, les moeurs des hommes et la biologie des anophèles concourent à créer l'ensemble de circonstances le plus favorable à l'efficacité du «house spraying».

Des exceptions peuvent évidemment être invoquées. Citons le cas d'ouvriers que l'un de nous a vu travailler de nuit, à Edéa, sur des gîtes à *A. gambiae,* ou le cas des pêcheurs de la Sanaga, que peuvent être contaminés sur les gîtes mêmes, ou pendant la nuit passée sous des abris rudimentaires. Toutefois, ces cas très spéciaux ne sauraient mettre en cause les principes généraux énoncés plus haut.

b) Rapports des indices malariométriques avec les espèces vectrices et leur densité.

La variété des facies écologiques fait que la faune anophèlienne diffère énormément, qualitativement et quantitativement d'un village à l'autre. Les indices malariométriques apparaissent en étroite corrélation avec l'anophélisme local. Nous en donnerons quelques exemples précis, provenant des enquêtes faites en 1955 dans des villages non traités et rapportées par Languillon, Mouchet, Rivola & Rateau (7); ils se répartissent en quatre catégories.

1.° — *Localités à très faible densité de vecteurs;* au village d'Oveng en Z. P. secteur C., des recherches quotidiennes, diurnes et nocturnes, poursuivies dans deux maisons pendant huit mois n'ont permis de capturer qu'un seul *A. gambiae* et la prospection au moins hebdomadaire des autres habitations n'a pas eu plus de succès. Or dans ce village les indices paludométriques des enfants étaient très faibles.

2.° — *Localités uniquement infestées de vecteurs naturels* (A. moucheti *et* A. nili).

Il s'agit, généralement d elocalités proches des grands et moyens cours d'eau. A la station témoin d'Ebogo (Z. P.) où *A. moucheti* est seul en cause, l'index plasmodique de l'enfant était de 80 %. Dans les mêmes conditions, il était de 79 % près de Lomié et de 43 % près de Méssamena.

3.° — *Localités fortement infestées par* A. gambiae *seul*

C'est notamment le cas de la plupart des grandes villes. L'endémie est alors essentiellement fonction de la densité des vecteurs. En Z. P.

l'index plasmodique de l'enfant était de 65 % à Ngoulemakong, de 47 % à Okola.

4.° — *Localités infestées par* A. gambiae *en association avec* A. moucheti *et* A. nili; ce sont celles où l'on observe les taux les plus élevés d'endémie, ce qui s'explique par la densité généralement plus forte des vecteurs. Morin avait déjà signalé ce phénomène en 1955 (10). A Mbammayo (Z. P. secteur B), où existait l'association d'*A. moucheti* avec *A. gambiae*, l'index plasmodique de l'enfant était de 66 %. Dans la région du Ntem, cet indice était de 81 % à Meyo Nkoulou (memê association de vecteurs) et de 79 % à Nyabessan (association *A. nili, A. moucheti* et *A. gambiae*).

c) *Durée de la transmission*

Dans ce pays où la température, relativement constante, permet l'accomplissement du cycle sporogonique des Plasmodium pendant toute l'année, la durée et l'intensité de la transmission dépendent essentiellement du cycle de densité des vecteurs, qui varie suivant les espèces.

Dans les localités où *A. moucheti* est dominant, la transmission, quoique d'intensité légèrement variable, s'étale tout au long de l'année, la densité de cet Anophèle étant toujours suffisante pour l'assurer.

Dans les localités où *A. gambiae* est le seul vecteur, la transmission suit les fluctuations de la densité de cet insect; c'est-à-dire qu'elle présente deux maxima très nets correspondant aux saisons de pluies.

Naturellement en cas d'association des deux principaux vecteurs, la transmission participe à la fois de l'un et l'autre processus, ci-dessus décrits, agissant synergiquement.

CHAPITRE III

L'Endémicité

Indices malariométriques de la région avant les campagnes de «house spraying»

Grâce aux travaux de Vaucel & Campourcy [(1943) (15)] et d'autres auteurs, on connaît bien la place importante que tenait le Paludisme dans la Pathologie du Cameroun, spécialement en zone forestière.

Yaoundè et ses environs étaient «tristement réputés pour la fréquence des accès pernicieux et des atteintes de fièvre bilieuse hémoglobinurique» et à l'hôpital de cette ville, de 1945 à 1949, 15 % des admissions de malades européens étaient dues au Paludisme [Morin, 1955) (10)].

a) *Endémicité dans la Zone Pilote*

Une enquête épidémiologique a été faite par Morin en 1953 (31) dans une région d'environ 50 000 habitants autour de Yaoundé; c'est précisément cette région qui devait, l'année suivante, devenir le théâtre de travaux à caractère expérimental (Zone Pilote de Yaoundé). Elle a comporté l'examen de 1 300 nourrissons et enfants; à l'occasion des extensions successives de la Z. P., deux enquêtes nouvelles ont été faites en 1955 et 1957 dans des régions non désinsectisées, concentriques de la précédente et ont donné des résultats analogues [(Languillon) (21 & 32)]. Les indices malariométriques fournis par ces enquêtes figurent sur le Tableau1 ci-après; ce sont ceux d'un Paludisme mésoendémique grave.

b) *Endémicité dans la Zone de Campagne Sud*

Dans le Tableau 2, sont résumés les résultats d'une enquête faite en 1955 dans six du Sud Cameroun; 2 234 sujets ont été examinés, uniquement dans des villages qui se trouvaient nettement en dehors des zones traitées par des insecticides à effet rémanent [(Languillon, Mouchet, Rivola & Rateau, 1956) (7)].

Les indices malariométriques présentés sur ce tableau correspondent dans trois Subdivisions à un Paludisme mésoendémique grave, partout ailleurs à un Paludisme hyperendémique. Des recherches complémentaires ont permis de noter, chez l'adulte, la régression parallèle des indices plasmodique et splénique, caractéristique du Paludisme holoendémique.

Toutefois il importe de signaler que ces tableaux synoptiques présentent des indices globaux, résultats des récapitulations. A lire le détail des protocoles d'enquête, en constate que la répartition du Paludisme est nettement hétérogène. Ainsi qu'il ressort des observations relatées au chapitre précédent, cette répartition est en étroite corrélation avec les différentes modalités de l'anophélisme.

TABLEU 1 — *Evolution de l'Endémicité Paustre dans la Zone Pilote de Yaoundé*

Localités et enquêtes	Indices malariométriques				
	Nourrisons		Enfants		
	Examinés	Indice parasitaire	Examinés	Indice splénique	Indice plasmodique
Secteur A: Villages traités depuis 1954					
Enquête pré-opérationnelle (Morin, 1953)	182	36,2	1.118	41,7	40,6
Enquêtes en cours de campagne, Nov.-Déc., 1957 ...	310	0,32	2.275	4,7	2,06
(Chastang), Avril-Mai, 1958	400	0	2.068	3,19	0,82
Secteur B: Villages traités depuis 1955-56					
Enquête pré-opérationnelle (Languillon, 1955)	139	27,4	634	33,9	29,3
Enquêtes en cours de campagne, Nov.-Déc., 1957 ...	124	6,4	991	5,3	5,3
(Chastang), Avril-Mai, 1958	164	1,8	715	3,9	1,53
Secteur C: Villages traités depuis 1957					
Enquête pré-opérationnelle (Languillon, 1957)	99	16	365	26	28,5
Enquêtes en cours de campagne, Nov.-Déc., 1957 ...	215	6,5	1.278	8,8	7,6
(Chastang), Avril-Mai, 1958	274	3.28	1.169	8,38	5,13

c) *Espèces plasmodiales*

Les examens parasitologiques pratiqués lors des enquêtes précédemment mentionnées, ont montré une prépondérance massive de *Plasmodium* falciparum (87,85 %). La fréquence de *P. malariae* a été de 11,13 % et celle de *P. ovale* de 1,02 %. *P. vivax* n'a jamais été observé.

Z. P. = Zone Pilote d'Expérimentation Antipalustre de Yaoundé.

TABLEAU 2 — *Endémicité malarienne avant le house spraying dans la Zone de Campagne Sud*

Régions	Indices malariométriques		
	Nourrisons	Enfants	
	Indice parasitaire	Indice splénique	Indice plasmodique
Région de Kribi	44	55	60
» du Ntem	50	74	72
» » Dja & Lobo	36	63	62
» » Haut-Nyong	20		
Subdivision de Lomié		60	74
» » Méssamena		36	34
Région du Lom & Kadei	60	54	70
» de la Boumba-Ngoko	25		
Subdivision de Yokadouma		44	46
» » Moloundou		31	21

SECONDE PARTIE

LA LUTTE ANTIPALUDIQUE

CHAPITRE IV

Organisation

Service autonome dans les grandes villes
Campagnes depuis 1954 en milieu rural

a) La ville de Yaoundé, capitale administrative du Cameroun, compte actuellement 56 000 habitants. Elle a depuis longtemps un service d'hygiène autonome qui pratiquait la lutte antilarvaire dès avant l'ère du large emploi des insecticides et procède depuis 1949 à des campagnes régulières de «house-spraying». De ce fait, elle a gardé son autonomie et ne s'est pas trouvée incluse dans les campagnes ultérieures.

La ville de Douala, port et capitale commerciale, a 120 000 habitants, auxequels s'ajoute une importante population flottante. Comme la précédente, cette ville est dotée d'un service d'hygiène autonome; celui-ci s.est d'abord consacré à la lutte antilarvaire, particulièrement importante dans cette grande agglomération construite sur un terrain à pente presque nulle. Le «house-spraying» a été logtemps fragmentaire, il est devenu systématique depuis 1956. Cette ville s'est trouvée également exclue des campagnes.

b) C'est en 1953 qu'ont commencé à s'instaurer les Campagnes antipaludiques avec Coopération internationale.

L'Organization Mondiale de la Santé leur assure l'assistance d'un Consultant paludologue. Le Fonds International de Secours à l'Enfance (F. I. S. E.) fournit une importante contribution en nature: insecticides, véhicules, pulvérisateurs. Les Gouvernements Français (F. I. D. E. S.) et Camerounais assument la charge du budget de fonctionnement. L'Office de la Recherche Scientifique et Technique Outre Mer met à leur disposition chercheurs et techniciens entomologistes.

Dans le Sud Cameroun, où les opérations d'aspersion ont débuté en 1954, on distingue:

— Un territoire restreint, destiné à permettre des observations entomologiques et épidemiologiques suivies et des applications d'insecticides à caractère expérimental; c'est la «Zone Pilote de Yaoundé» (Z. P.) dont les transformations succéssives seront relatées au chapitre suivant.

— Une campagne de masse dite «Campagne Sud» qui couvre maintenant neuf Régions administratives: Sanaga Maritime, Kribi, Ntem, Mbam, Hyong et Sanaga, Dja & Lobo, Haut-Nyong, Lom & Kadéi, Boumba-Ngoko. Il est important pour le développement ultérieur de cet exposé (Chapitre VI) de noter que les termes «Zone de Campagne Sud» et «Zone forestière» du Sud Cameroun ne peuvent être tenus pour synonymes. En effet des régions nettement forestières (Nkam, Mungo, Wouri) n'y sont pas comprises. Par contre, comme il a été impossible d'assigner à la Campagne d'autres bornes que les limites administratives, les organisateurs se sont vus contraints d'y inclure de vastes territoires qui ne présentent pas un facies forestier: majeure partie du Mbam, du Lom & Kadéi, nord est du Nyong & Sanaga.

CHAPITRE V

Les Travaux à caractère expérimental

Technique, résultats et perspectives de la lutte antipaludique dans la Zone Pilote de Yaoundé

a) *Historique*

Au début des opérations, la zone pilote se limitait à une région de 50 000 habitants environ, autour de Yaoundé. Le premier protocole expérimental consistait en une tentative d'utilisation des divers insecticides de contact en ordre dispersé. Les villages étaient traités isolément, tantôt au D. D. T. selon 3 dosages distincts, tantôt à la Dieldrine, tantôt au H. C. H. [(Morin, 1953/55) (31)]. Ultérieurement, se fit une certaine extension en ilôts qui porta la population de la Zone à 70 000 habitants environ. En même temps, les aires d'essai de chaque insecticide devenaient plus homogènes [(Najera, 1955/56) (32)].

Durant ces trois premières années, les aspersions gardèrent toujours un caractère fragmentaire; dans une région déterminé, on ne put jamais parvenir à traiter tous les villages, pas plus que, dans les villages, on ne put atteindre toutes les habitations. Une étude minutieuse a permis de calculer que la proportion de population protégée variait de 50 à 60 % [(Livadas, Languillon & Coll., 1957) (33)].

b) *Travaux actuels*

Réorganisée à partir de Mars 1957 [(Livadas, Languillon & Coll., 1957) (33)], la Z. P. mesure actuellement 60 km d'Ouest en Est et 100 k du Nord au Sud; elle compte 120 000 habitants. Elle englobe la Zone originelle, les extensions ultérieures et les contrées intermédiaires. Elle comporte, par conséquent, trois catégories de villages: les uns traités depuis 1954 (Secteur A de la carte), les autres depuis 1955 ou 56 (Secteur B), les derniers depuis 1957 (Secteur C). Les techniciens responsables considèrent qu'il est d'une importance primordiale d'obtenir un traitement rigoureusement complet. Une connaissance parfaite de la région (recensement, topographie), un contrôle rigoureux, presque quotidien, des équipes sur le terrain, l'obligation pour celles-ci de se rendre dans toutes les agglomérations, y compris les hameaux accessibles seulement par sentiers pédestres, enfin des tournées de «rattrapage» pour traiter les habitations trouvées fermées lors d'un premier passage, sont autant de moyens qui ont permis d'atteindre ce but.

Les techniques d'emploi des insecticides se réduisent à deux: la moitié occidentale de la Z. P. est traitée au D. D. T. (poudre mouillable à 75 %, dosage de 2 g de produit technique au m^2, deux aspersions par an); la moitié orientale est aspergée à la Dieldrine (poudre mouillable à 50 %, dosage de 0,60 g de produit par m^2; une aspersion par an, au moins en principe).

Depuis sa réorganisation, la Z. P. a reçu:

—Un traitment complet des deux parties en Mai-Juin 1957;
—Un traitment de la partie D. D. T. en Janvier-Février 1958;
—Un traitment de la partie Dieldrine en Mars-Avril 1958, le délai d'un an ayant été ramené à 10 mois à la suite des constations entomologiques.

c) *Résultats épidémiologiques:*

Des enquêtes épidémiologiques de contrôle sont effectuées régulièrement deux fois par an; les deux dernières ont eu lieu: l'une six mois après le traitment de 1957, en Novembre et Décembre 1957; l'autre, un an après ce traitement en Avril et Mai 1958 Les résultats de ces deux enquêtes sont présentés secteur par secteur sur le Tableau 1 [(Chastang, 1958) (34)].

A la lecture de ce tableau il apparaît:

1) Que dans la portion originelle de la Z. P., soumise à l'influence des insecticides pendant trois années consécutives (1954 à 1956) et traitées de façon complète depuis pendant une année, *la transmission du Paludisme touche à son point terminal* (Secteur A).

2) Que dans le Secteur B soumis à l'influence des insecticides durant un ou deux ans selon les endroits (1955/56) et traité de façon

complète depuis une année, les indices malariométriques accusent une chute considérable qui laisse penser que la transmission du Paludisme s'y trouve très près de son point terminal.

3) Que dans le Secteur C, traité pour la première fois en 1957, les indices malariométriques marquent après une seule année de traitement complet, une chute très significative.

Il faut ajouter qu'il n'a été noté aucune différence entre les résultats constatés dans la partie aspergée au D. D. T. et ceux observés dans la partie traitée à àla Dieldrine.

d) Intérruption future des aspersions

Ces faits permettent d'envisager pour un proche avenir (probablement en 1960) l'interruption des opérations de désinsectisation dans une partie de la Z. P., voire dans sa totalité. On pense par conséquent que le moment est venu de commencer à organiser un système de surveillance épidémiologique qui se substituerait au programme de «house-spraying» dans la Z. P. et fournirait en même temps de précieuses indications sur la tactique à suivre, dans l'avenir, sur le reste du territoire.

CHAPITRE VI

Les Travaux en Campagne de Masse

Considérations générales sur l'état actuel de l'endémicité palustre dans la ville de Yaoundé et le Sud Cameroun

a) La situation dans la capitale du Cameroun est aussi favorable que possible. Les résultats des enquêtes épidémiologiques [(Languillon, 1957) (33); (Chastang, 1958) (34)] rejoignent les constattations des cliniciens: il est devenu tout à fait exceptionnel de trouver des hématozoaires dans un frottis de sang et dans ces très rares cas de Paludisme confirmé, l'interrogatoire permet toujours d'établir que la contamination a eu lieu «en brousse». *On peut donc affirmer que dans la ville de Yaoundé la transmission du Paludisme est totalement interrompue.*

b) *Dans la Zone de Campagne Sud,* [1] le chiffre de population protégée était, au début des opérations de 327 000 personnes. Tant par l'extension de son territoire que par une pénétration rurale de plus en plus poussée, cette Campagne protège maintenant 750 000 personnes. Cependant, et bien que cette règle souffre des exceptions de plus en plus nombreuses, le travail des équipes reste généralement tributaire des routes et des pistes accessibles aux véhicules. De la sorte, près de 200 000 individus environ demeurent en dehors de notre rayon d'action.

L'insecticide employé depuis 1954 jusqu'en 1956 a été le D. D. T. (poudre mouillable 75 %, au dosage de 2 g d'isomère pp' soit 3,9 g de produit commercial par m²) à raison de deux aspersions par an. Depuis 1957, on lui a substitué la Dieldrine, au même dosage et au même rythme que dans la Z. P.

c) *Résultats épidémiologiques de la Campagne Sud*

Dans ce pays, où, comme on l'a vu, le Paludisme était naguère soit mésoendémique, soit, plus généralement hyperendémique, et holoendémique, l'efficacité du «house-spraying s'est avérée partout indiscutable et les dernières enquêtes épidémiologiques montrent une regression générale des indices malariométriques. Cependant, la qualité des résultats obtenus, varie nettement selon les lieux [(Chastang, 1958) (34)].

Dans les régions de forêt dense, présentant un facies écologique analogue à celui de la Z. P., on constate un abaissement massif des indices, devenus inférieurs à 10 %. C'est le cas du Ntem, du Dja & Lobo, du Haut-Nyong et de la majeure partie du Nyong & Sanaga. On parvient même en certains endroits à trouver, sur plusieurs containes de frottis de sang, un indice parasitaire du nourrisson inférieur à 1 % (Sangmélima).

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[1] Une étude détaillée des travaux et des résultats de cette campagne sera publiée prochainement par l'un de nous.

La diminution des indices est importante mais moins spectaculaire:

1) Dans des sites de superficie restreinte, enclos dans la région forestière, mais présentant des caractères géographiques, agricoles, et humains particuliers (C'est le cas des rives grands cours d'eau avec pêcheries, des terres rizicoles, etc.).

2) Dans les parties périphériques de la campagne, limitrophes de régions ou de pays étrangers non désinsectisés.

3) Enfin, dans des régions rattachées à la Campagne Sud, mais n'appartenant plus à la zone forestière proprement dite: majeure partie du Ntem, du Lom & Kadéi, Nord-Est du Nyong & Sanaga.

On est donc amené à penser que dans la Zone forestière *sensu stricto,* si on disposait de moyens matériels permettant un travail «en profondeur» aussi complet que dans la Z. P., *on obtiendrait un résultat équivalent, c'est-à-dire l'arrêt de la transmission du Paludisme.*

Cette possibilité technique demeure malheureusement dans le domaine théorique. Son passage sur le plan pratique exigerait d'importantes dépenses supplémentaires ainsi que l'instauration de mesures efficaces contre l'apport de virus extérieur.

CHAPITRE VII

Observations entomologiques

I. Influence des traitements insecticides sur le comportement des principaux vecteurs
II. Effets généraux des traitements insecticides

I

a) *A. funestus* semble avoir été éradiqué de la région forestière, ni larve, ni imago n'yant été rencontré depuis 1955.

b) *A. gambiae* a disparu de Yaoundè; les recherches systématiques faites avec la collaboration du Service d'Hygiène Urbaine n'ont plus permis de récolter ni larve, ni imago depuis 1955.

A Douala, après les traitements insecticides complets, ce vecteur avait disparu des habitations et une semaine de prospection en saison de pluies ne faisait plus découvrir que deux gîtes larvaires, alors qu'on en trouvait auparavant des centaines [(Mouchet, 1955/56) (22 & 23); (Gariou, 1957) (19); (Rateau, 1957) (35)]. Par contre, *A. gambiae* demeurait abondant dans de nombreux villages périphériques non désinsectisés, qui constituaient une menace de réinvasion. Celle-ci s'est effectivement produite en 1958, à la faveur d'un fléchissement des opérations d'aspersion et une récente propection a fait découvrir de nouveau *A. gambiae* dans le quartier de Kassalafam [(Mouchet, 1958) (27)].

Dans la Z. P., depuis plus d'une année, les recherches systèmatiques, diurnes et nocturnes, dans les maisons, sont demeurées sans résultat et il n'a pas non plus été recensé de gîtes larvaires dans ce secteur [(Gariou, 1958) (20)].

Enfin, dans le vaste territoire de la Campagne Sud, où il n'a pas été possible de faire autre chose que des sondages, d'ailleurs nombreux, ni de jour ni de nuit, aucun imago n'a été trouvé dans les maisons traitées. Quelques gîtes larvaires ont été découverts, surtout à la périphérie de la forêt: Kikot sur la Sanaga, Dea près de Nanga Eboko. Imagos et larves persistent dans les agglomérations non traitées: au delà de Deng-Deng par exemple [(Mouchet, 1958) (25)].

Ces résultats et notamment la diminution considérable (ou la disparition) des gîtes larvaires, prouvent que *la population totale d'A. gambiae a été touchée* et en bien des localités éliminée, par le «house-spraying». Il est actuellement impossible de parler d'éradication, car *A. gambiae* persiste dans les villages non traités; d'autre part, nous ne pouvons affirmer que, même dans les agglomérations les mieux désinsectisées, des gîtes cachés ne subsistent pas, à partir desquels une recolonisation serait possible; pourtant nous ne croyons guère à une telle éventualité, sauf cas exceptionnels.

Des résultats aussi spectaculaires sont dus, comme nous l'avons déjà souligné, à un concours de circonstances exceptionnellement favorables, qui tiennent tant aux moeurs humaines qu'à la biologie des Anophèles. Ce sont:

1) Le fait qu'étant données les conditions nécessaires à l'établissement de ses gîtes larvaires, *A. gambiae*, ne peut, en forêt, s'éloigner des lieux habités;

2) Que dans les villages où accèdent les équipes d'aspersion, toutes les maisons peuvent être traitées (une seule exception, rare et déjà citée, les abris temporaires nécessités par la pêche ou certaines cultures);

3) Que l'anthropophilie du vecteur se trouve renforcée par l'absence de gros bétail; elle devient presque obligatoire;

4) Que, de même, son entophagie devient également presque obligatoire, les habitants étant, la nuit, d'habitudes casanières;

5) Qu'étant donné son entophilie, il a peu de chances de trouver pour s'y reposer, une surface indemne de dépôt toxique.

Dans ces conditions *A. gambiae* ne pouvait échapper aux effets des traitements insecticides dont il est devenu la victime de choix. Cette situation est, évidemment, toute différente de celle qui se rencontre en savane, où ce vecteur possède de très nombreux gîtes naturels et a la possibilité de subsister, au moins partiellement, en dehors de tout contact humain [(Holstein, 1951) (6)].

c) Les imagos d'*A. moucheti* n'ont pratiquement plus été capturés dans les habitations sur le territoire de la Z. P. A Meyo-Nkoulou (Ntem) nous avons observé des entrées beaucoup moins fréquentes que lors de notre prospection de 1955 avant le traitment, et dans les mêmes maisons nous avons trouvé le matin, à terre, des imagos morts [(Mouchet, 1958) (24)].

Dans la Z. P. aussi bien que dans les autres régions désinsectisées du Sud, on cotinue à récolter des larves. [(Gariou, 1958) (20); (Mouchet, 1958) (24)]. Cette persistance s'explique par le fait qu'une partie de la population d'*A. moucheti,* moustique forestier, peut se maintenir en dehors de tout contact humain et assurer la perennité de l'espèce. La persistance ou l'absence des entrées dans les maisons dépend, au moins en partie, de la proximité et de la richesse des gîtes larvaires. Cependant on a récemment observé, à Nsimalen (Z. P.), que les *A. moucheti* produits par des gîtes larvaires très peuplés n'entraient pas dans les maisons pourtant proches [(Gariou, 1958) (20)]; peut-être existe-t-il plusieurs biotypes de l'espèce?

La persistance d'*A. moucheti* (comme celle de nombreux autres vecteurs un peu partout dans le monde) ne constitue pas un obstacle à la réussite des opérations de «house-spraying»; le but que celles-ci se proposent, en effet, *n'est pas l'éradication du vecteur, mais l'arrêt de la transmission du Paludisme.*

d) Les imagos d'*A. nili* n'ont plus été capturés au cours des prospections systématiques en Z. P depuis 1955.

A Nyabessan (Ntem) nous avons observé des entrées dans les habitations aspergées; au matin aucun *A. nili* n'a été trouvé sur les murs, mais des cadavres jonchaient le sol [(Mouchet, 1958) (24)].

Les larves de cet anophèle persistent dans la plupart des cours d'eau de la région forestière, en Z. P. comme en Zone de Campagne Sud. Ce qui a été dit à propos d'*A. moucheti,* sur le maintien d'une partie de la population anophélienne, est probablement vrai, également, pour cette espèce. Ici, plus encore que pour l'espèce précédente, l'existence de différents biotypes semble devoir être postulée.

Rien ne permet d'affirmer que *A. nili* est encore un vecteur effectif dans les régions traitées de la zone forestière.

II

Effets généraux des traitements insecticides

Il n'a pas été possible de faire des observations précises sur le comportement d'*A. gambiae* et *A. funestus* après les traitements insecticides, les stations s'étant trouvées dépeuplées avant les expérimentations prévues. Toutefois on peut conclure a posteriori que ces moustiques n'ont pas évité le contact des insecticides muraux (D. D. T. & Dield.) et qu'ils y ont été très sensibles. Aucune modification de comportement n'est intervenue, sans quoi on aurait assisté dans les localités traitées au maintien, au moins partiel de la population anophèlienne.

L'effet des insecticides sur *A. moucheti* est étudié dans deux maisonnettes («cases expérimentales») à Ebogo (Z. P. Secteur témoin). L.une a été aspergée à la Dieldrine et l'autre au D. D. T. alors que le reste du village n'est pas traité. Les gîtes larvaires de cette station, situés dans le fleuve Nyong, sont riches et distants de moins d'un kilomètre du village. La densité des imagos dans les habitations est supérieure à 10.

Il a été observé que *l'effet répulsif* de l'un et l'autre insecticide ne dépasse pas 36 heures. Passé ce temps, les anophèles entrent normalement dans les maisonnettes traitées, en aussi grand nombre ou presque que dans les maisons non traitées.

Il semble que *l'effet irritant,* qui pousserait les moustiques à abréger leur séjour sur les parois toxiques, soit ici peu sensible. Les anophèles capturés dans les pièges extérieurs des cases expérimentales sont proportionnellement moins nombreux qu'avant la désinsectisation, la plupart d'entre eux étant morts ou malades avant d'avoir pu sortir. Lorsque l'insecticide commence à perdre son efficacité, les sorties dans les pièges extérieurs (pièges vérandas) sont plus nombreuses [(Gariou, 1958) (20)].

Il n'y a donc apparemment pas de modification du comportement. Dans les maisons expérimentales, il semble que tous les *A. moucheti* qui entrent, prennent contact avec le toxique mural et soient tués.

La mort des moustiques intoxiqués survient très rapidement (moins d'une heure) lorsque l'application des insecticides est récente. Quelques mois plus tard (3 ou 4) la durée de survie, s'allonge et peut atteindre 24 heures. A quelques différences de détail près, le processus est le même pour le D. D. T. et la Dieldrine.

Sur les murs en terre des maisons des environs de Yaoundé (Ebogo, Fegmimbang, Ekombitié), la remanence du D. D. T. a bien la durée de 6 mois sur laquelle nous comptions. La rémanence de la Dieldrine est moins précisément fixée; elle est, en tout cas, très certainement inférieure à un an.

Enfim, *aucun phénomène de résistance aux insecticides* (D. D. T. ou Dieldrine(n'a été observé jusqu'ici avec les Anophèles vecteurs.

CONCLUSIONS

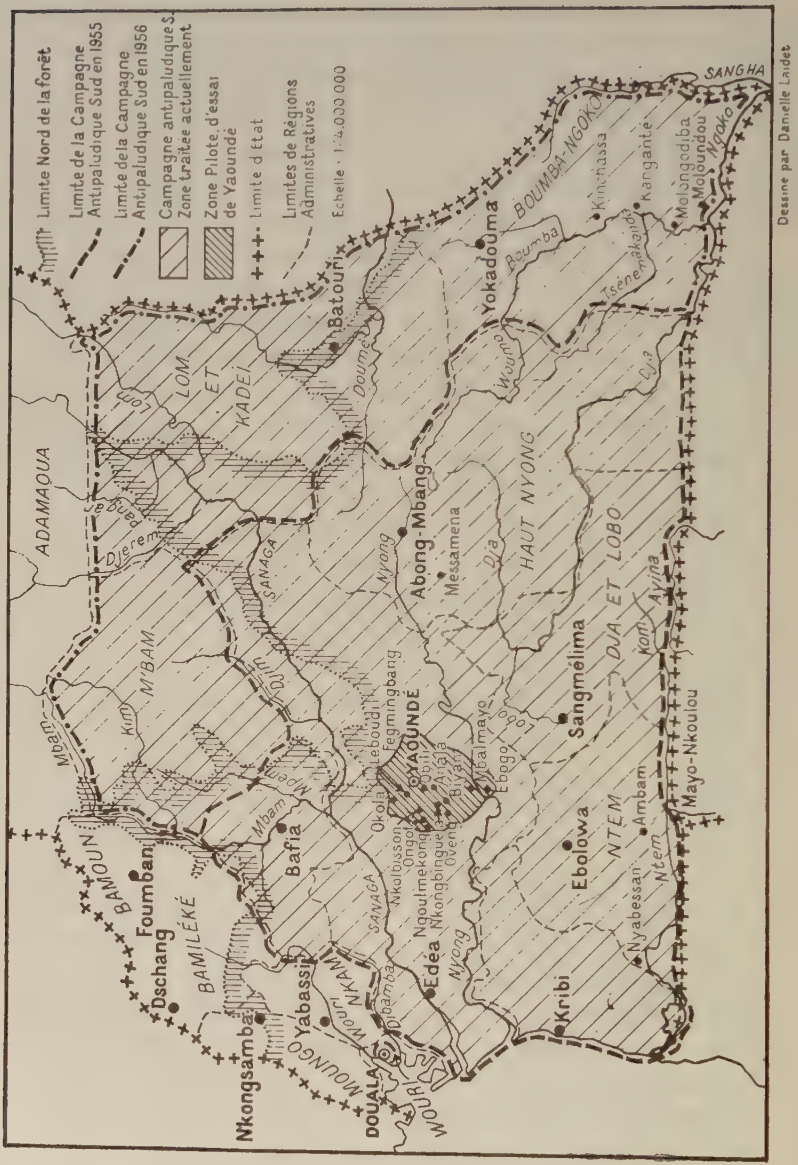
De l'exposé qui précède on peut tirer les conclusions suivantes:

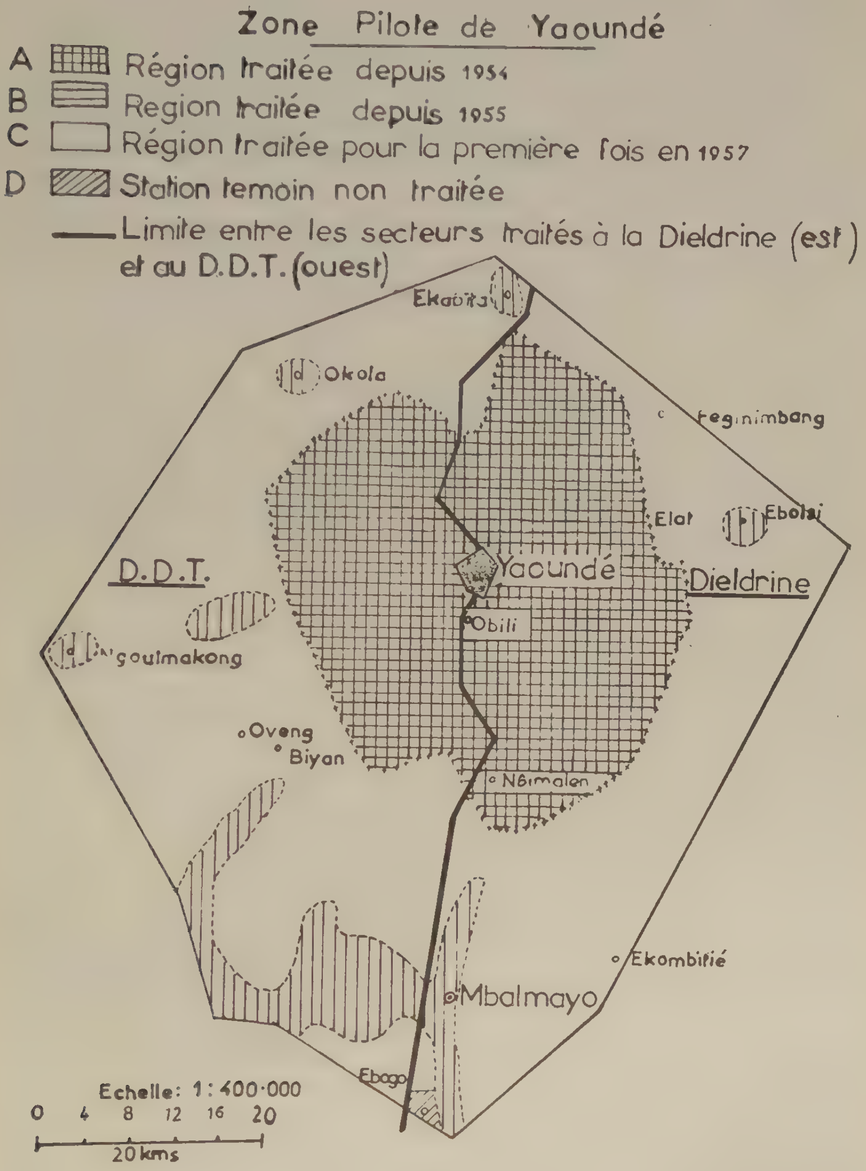
1 — Dans la Zone Pilote de Yaoundé, la Lutte Antipaludique par le seul «house-spraying» aboutit à un incontestable succès. Selon l'ancienneté du traitment des secteurs on constate l'arrêt d ela transmission, ou on l'entrevoit.

2 — Dans la Zone de Campagne Sud, on enregistre une diminution massive des indices, réduits au taux d'une hypoend'micité restreinte, au moins dans les régions de forêt dense et là où les aspersions sont faits depuis assez longtemps.

CARTE DU SUD-CAMEROUN

CAMPAGNES ANTI-PALUDIQUES ET ÉTUDES ENTOMOLOGIQUES


Limite Nord de la forêt
Limite de la Campagne Antipaludique Sud en 1955
Limite de la Campagne Antipaludique Sud en 1956
Campagne antipaludique S. Zone traitée actuellement
Zone Pilote, d'essai de Yaoundé
Limite d'État
Limites de Régions Administratives
Echelle : 1/4.000 000
Dessiné par Danielle Laidet
ADAMAOUA
LOM ET KADEI
Lom
Batouri
Doumé
Djerem
Pangar
BOUMBA-NGOKO
Yokadouma
Boumba
Kinchassa
Kangantè
Molongodiba
Moloundou
Ngoko
SANGHA
Tsénémakaïda
Wouna
Dja
HAUT NYONG
Abong-Mbang
Messamena
Nyong
SANAGA
Djim
M'BAM
Kim
Mbam
Mpem
Bafia
BAMOUN
Foumban
BAMILÉKÉ
Dschang
Nkongsamba
Yabassi
MOUNGO
Wouri
NKAM
Dibamba
DOUALA
WOURI
Edéa
Nyong
Ngoulmekong
Nkongbingué
Nkolbisson
Ongot
Okola
Leboudi
Fegmingbang
YAOUNDÉ
Obili
Ahala
Biyan
Oveng
Mbalmayo
Ebogo
Lobo
Sangmélima
DJA ET LOBO
Kom
Ayina
Ebolowa
NTEM
Ambam
Ntem
Nyabessan
Mayo-Nkoulou
Kribi


Zone Pilote de Yaoundé
A ▦ Région traitée depuis 1954
B ▤ Region traitée depuis 1955
C ☐ Région traitée pour la première fois en 1957
D ▨ Station temoin non traitée
— Limite entre les secteurs traités à la Dieldrine (est) et au D.D.T. (ouest)
Ekabita
b
Okola
d
Feginimbang
c
Elat
Ebolai
b
D.D.T.
Yaoundé
Dieldrine
Obili
N'goulmakong
d
Oveng
Biyan
Nsimalen
Ekombitié
Mbalmayo
Ebogo
d
Echelle: 1 : 400·000
0 4 8 12 16 20
20 kms

3 — L'amélioration est nette, mais moins importante, dans les contrées où les caractères géographiques, écologiques ou humains sont différents.

En dernière analyse, on peut dire que dans la région forestière sensu stricte l'éradication du Paludisme est techniquement réalisable.

L'accomplissement d'une telle tâche ne serait pas sans poser d'importants problèmes mais ceux-ci sont exclusivement d'ordre administratif et budgétaire.

Peut-être ces conclusions s'avèreront-elles valables pour d'autres pays d'Afrique tropicale où les conditions géographiques sont identiques.

RÉSUMÉ

Dans la première partie les auteurs tracent une esquisse rapide de l'endémie palustre, de ses vecteurs et de ses modes de transmission dans le Sud Cameroun. La seconde partie donne un aperçu des résultats obtenus dans les domaines épidémiologiques et entomologiques à la suite des applications des insecticides.

Cet article se divise en sept chapitres:

Le Chapitre I traite des caractères physiques et écologiques du pays, de l'habitat humain, très sédentaire, et des habitudes de la population.

Le Chapitre II expose la biologie des quatre espèces d'Anophèles vecteurs: *A. gambiae*, lié étroitement à l'homme, tant pour sa subsistance que pour l'établissement de ses gîtes larvaires, est surimposé dans la forêt, comme *A. funestus* qui n'y a eu qu'une pénétration réduite. Tous deux sont anthropophiles et entophilos, au moins pendant une partie de leur cycle. *A. moucheti* est au contraire un vrai moustique forestier; il colonise des gîtes naturels; il présente un haut degré d'anthropophilie et d'entophilie. La biologie *d'A. nili*, moins connue, se rapproche de celle de l'espèce précédente.

Les modalités de la transmission du Paludisme sont évoquées.

Le Chapitre III relate, qu'avant les traitements insecticides, il régnait partout une mésoendémicité grave ou une hyperendémicité avec holoendémicité.

Le Chapitre IV décrit l'organisation de la lutte antipaludique par application des insecticides à Yaoundé, à Douala, dans la Zone Pilote et dans la Zone de Campagne Sud. Ce programme est exécuté en collaboration, par l'O. M. S., l'E. I. S. E., l'O. R. S. T. O. M. et le Service de Santé local.

Le Chapitre V retrace les opérations successives effectuées dans la Zone Pilote; celle-ci est actuellement traitée par moitié à la Dieldrine et au D. D. T. Les plus récents indices paludométriques montrent que, dans la partie la plus anciennement traitée, la transmission est pratiquement interrompue. Pas de différence entre les résultats de la partie D. D. T. et de la partie Dieldrine.

Le Chapitre VI donne les résultats de l'application des insecticides à Yaoundé et dans la Zone de Campagne Sud (D. D. T. puis Dieldrine depuis une année). Les résultats sont excellents en pleine zone forestière, moins bons sur les pourtours et dans les régions de forêt-galeries.

Le Chapitre VII fournit les résultats des observations entomologiques après l'application des insecticides. *A. funestus* est pratiquement éradiqué. *A. gambiae* a disparu des habitations et ses gîtes larvaires ont considérablement régressé. *A. moucheti* a pratiquement disparu des maisons ainsi que *A. nili* mais lours larves persistent. Des expériences faites sur *A. moucheti* on déduit que, l'effet répulsif du D. D. T. et de la Dieldrine est très court, que l'effet irritant se manifeste peu, dans des conditions très proches des conditions naturelles et que le comportement du vecteur n'est pas modifié. Nulle part n'a été observée de résistance à ces insecticides chez les Anophèles.

Les auteurs concluent que l'Eradication du Paludisme dans la zone forestière du Sud Cameroun est techniquement réalisable et dépendrait plutôt de la solution de lourds problèmes administratifs et financiers.

De telles conclusions, sont, peut-être, valables pour d'autres régions centrafricaines présentant des conditions analogues.

Organisation Mondiale de la Santé, Fonds des Nations Unies pour l'Enfance, Office de la Recherche Scientifique et Technique Outre Mer, Ministère de la Santé Publique du Cameroun et Service d'Hygiène Mobile et de Prophylaxie.

SUMMARY

In the first part of this paper an outline is given of the malaria endemicity, the vectors and the modalities of malaria transmission in the Forest area of South Cameroons. The second part deals with the results achieved on epidemiological and entomological grounds by the application of the insecticides. The paper is divided into seven chapters:

Chapter I contains a short review of the physical and ecological characters of the region concerned as well as of the habitat and the customs of the population.

Chapter II deals with the biology of the four anopheline vectors: *A. gambiae*, bound strictly with man for its maintenance as well as for the establishement of its breeding places, is superimposed to the forest, like *A. funestus* which however has a very limited penetration. Both species are anthropophilic and endophilic, at least during one part of their cycle. *A. moucheti* on the contrary is a real mosquito of the forest. It settles natural breeding places and has a high degree of anthropophily and endophily. The biology of *A. nili*, less known, ressembles to that of the previous species.

Modalities of malaria transmission are recalled.

Chapter III relates that before insecticide applications a severe mesoendemicity or a hyperendemicity with holoendemicity were prevailing in the region.

Chapter IV sets out the organization of the antimalaria campaign carried out with the application of insecticides in Yaoundé, Douala, the Pilote Zone and in the South Cameroons campaign Zone in collaboration with W. H. O., U. N. I. C. E. F., O. R. S. T. O. M. and the local Public Health Service.

Chapter V deals with the successive phases of malaria operations in the Pîlot Zone. Actually this zone is treated half by D. D. T. and half by Dieldrin. The last malariometric data show that in the older part of the above zone malaria transmission has been practically interrupted. There is no difference of results between the D. D. T. and Dieldrin sectors.

Chapter VI gives the results obtained by insecticide applications in Yaoundé and in the South Cameroons campaign Zone.

In the last case D. D. T. was first used and one year ago Dieldrin. The results are very gratifying in the forest area while are less satisfactory in the periphery and in the areas of forest-galeries.

Chapter VII yields the results of entomological observations after the application of insecticides. *A. funestus* apparently has been eradicated. *A. gambiae* has disappeared from houses and its breeding places are considerably reduced. *A. moucheti* has practically disappeared from houses as well as *A. nili* but their breeding places persist. The experiments conducted with *A. moucheti* showed that the repulsif action of both Dieldrin and D. D. T. is of a very short duration (about 36 hours). On the other hand the irritant effect under conditions very similar to natural ones is very little pronounced and there is no modification of the comportment of the vector. Resistance to insecticides nowhere has been observed.

The authors conclude that eradication of malaria in the Forest area of South Cameroons is technically feasible and that it would rather depend from the solution of the heavy problems of administration and finance.

These conclusions might be applied to other regions of Central Africa in which similar conditions prevail.

SOMMARIO

Nella prima parte si dà una rapida descrizione dell'endemia malarica, dei vettori e dei modi di trasmissione della malaria nel Sud-Camerun. Nella seconda parte sono esaminati i risultati ottenuti nel dominio epidemiologico e entomologico, in seguito alla applicazione degli insetticidi. L'articolo si divide in 7 capitoli:

Il Capitolo I tratta dei caratteri fisici e ecologici del paese, del habitat umano e delle abitudini della popolazione.

Nel Capitolo II è esposta la biologia delle quattro specie vettrici: L'*A. gambiae,* legato strettamente all'uomo, tanto per la sua sussistenza, quanto per lo stabilimento delle sue gite larvali, è una specie sopraimposta nella foresta, come l'*A. funestus,* il quale peró ha una penetrazione molto limitata. Queste due specie sono antropofile e endofile, almeno durante una parte del loro ciclo. L'*A. mou-*

cheti è al contrario una vera zanzara forestale; colonizza delle gite naturali e presenta un alto grado di antropofilia e endofilia. La biologia del l'*A. nili*, meno conosciuta, rassomiglia a quella della specie precedente. In seguito sono evocate le modalità della trasmissione della Malaria nella regione in questione.

Nel Capitolo III sono riferite le condizioni che esistevano prima dei trattamenti con gli insectticidi; dapertutto regnava una mesoendemia grave o una iperendemia accompagnata da oloendemia.

Nel Capitolo IV viene descritta l'organizazione della lotta antimalarica per mezzo degli insetticidi nelle città di Yaoundé e Douala, nella Zona Pilota, e nella Zona della campagna del Sud-Camerun. Questo programma è applicato in collaborazione dell'O. M. S., dell'U. N. I. C. E. F., dell'O. R. S. T. O. M. e del Servizio locale di Sanità Publica.

Nel Capitolo V sono rintracciate le operazioni, successive effetuate nella Zona Pilota; essa attualmente viene trattata nella sua metà con la Dieldrina e nell'altra metà con il D. D. T.; I più recenti indici malariometrici mostrano che nella parte più anticamente trattata di questa zona, la trasmissione della malaria è pratticamente interotta. Non si notano differenze tra i risultati della parte trattata con Dieldrina e di quela trattata con il D. D. T.

Nel Capitolo VI si danno i risultati della applicazione degli insectticidi à Yaoundè, e nella zona della Campagna del Sud-Camerun. In quest'ultimo caso venne usato il D. D. T. e ultimamente la Dieldrina. I risultati si mostrano eccellenti in piena zona forestiera e meno buoni nei bordi della foresta e nelle galerie forestali.

Nel Capitolo VII sono esposti i risultati delle osservazioni entomologiche dopo l'applicazione degli insetticidi. L'*A. funestus* apparentemente è stato eradicato. L'*A. gambiae* è scomparso dalle abitazioni e le sue gite larvali sono considerevolmente ridotto. L'*A. moucheti* è pratticamente scomparso dalle case, come pure l'*A. nili*, ma persistono le loro gite larvali. Dagli esperimenti fatti sull'*A. moucheti* risulta che l'effetto ripulsivo dei due insetticidi (D. D. T. e Dieldrina) è di molto breve durata (circa 36 ore), e l'effetto irritante è poco manifesto in condizioni prossime a quelle naturall. D'altronde il comportamento del vettore non ha subito alcuna modificazione. Non è stato constatato il fenomeno della resistenza agli insetticidi.

Gli autori concludono che l'eradicazione della malaria nella zona forestale del Sud-Camerun è technicamente realizzabile essa dipenderebbe piuttoste dalla soluzione dei gravi problemi amministrativi e finanziari.

Queste conclusioni potreblero forse valere anche per altre regioni dell'Africa Centrale che si trovano in condizioni analoghe.

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ANTIMALARIA CAMPAIGN IN IRAN

Dr. Farman Farmaian (Iran)

Mr. President, Ladies, Gentlemen:

I am not going to take much of your time in these last minutes of our session to read you a full report on antimalaria campaign and activities in Iran.

May I just say that a very continuous and sustained effort has been taking place in Iran during these recent years.

The control program for malaria started in 1948-49 with a fair size pilot project was extended gradually to cover in the last 3 years the whole malarious areas of the country estimated at 26 000 villages with a population of 8 ½ million inhabitants within this areas.

After necessary preparation, as a pre-eradication phase in 1957, this year we started our eradication scheme, including discontinuation of spraying operations and establishement of 100 % surveillance and chemotherapy in some limited but wide areas of the country. The points I wish to make is not about the details of the program, its present results, etc., but I believe you may be interested to know some aspects of the difficulties and problems which we usually meet and can be placed by any one working under similar conditions.

These «area problems» (different from those of a purely technical character, resistance-sorption, etc.) are nevertheless specific in nature but intimately linked with the area, its ground, its habit, its tradition, its civilisation.

To save time I am just going to list below some of these problems. Most of them are in fact common to many other countries; but likely the degree of importance and specificity will vary in relation to area and time.

1) So for Iran to day, among these area problems, one of the utmost importance is the one derived from the existence of nomadic tribes and their transhumance habit.

At this point may I remind you that Iran is a large mountainous country (1 600 000 km²) with a total population of 20 million inhabitants of which approximately 3 millions live a nomadic and tribal life. These form an unsettled or in some places half settled population with different habits and custom, each forming a community within the community.

This nomadic problem, as far as malaria eradication is concerned, has grown from a minor state gradually in magnitude to become our main headache to day at the point where we stand in the completion of our eradication campaign. This illustrates very well the variation of these area problem according to time as mentioned.

2) Town malaria foci I am speaking of medium size towns, of 15 to 40 000 inhabitants. Usually we do not, and we cannot afford to, spray towns except when of a small size less than 10 000 inhabitants; and located in or near a hyperendemic zone. In places where sanitary programs for some reasons or other have been postponed or have not advanced at a speed in concordance with the eradication scheme a serious problem arises. We have reached in our program a position where the country around a town and its peripheric belt are clear of malaria but in the town itself pools, disused wells, unkept garden canals, ditches, open irrigation and rain channels, drains, all unsanitary conditions form the most attractive and variable breeding sites; not to mention the unsprayed, unscreened houses favourable as adult resting places.

3) Temporary summer huts made of mud or straw or a mixture of the two. These huts are used by cultivators, field laborers, fishermen, crop and fruit pickers, hunters, etc., for short duration at various intervals of time.

4) Agricultural problems. Establishment of small size dams to help irrigation or water mills. Extension of rice fields promoted by better health conditions through malaria control work of recent years.

5) Opposition to spraying in view of the protection of bee-hives and silk worm or stored crops.

Many peasants, in Iran, use also their house for storage of tobacco leaves, tea leaves, corns, oignons which are hurry from the ceiling. Others make a living by preparing dried fruits. The fruits are tied for grafes (raisins and figs) and hurry from the ceiling. For apricots and peaches shelf-like spaces are provided in the side walls. Besides in many areas rice and flour, a whole year's ration, is kept and stored in huge lose-cover containers. On many occasions anopheles mosquitoes have been captured inside these containers.

6) Oppositions to the collection of blood samples and film slides from children and even adults at frequent intervals. This opposition is increased and extends from a family to a whole village if other ailments are not cared or disregarded by the blood collector.

7) Frequently it is impossible to check with regularity a previous blood positive case or a sick suspect with negative blood. Mostly when the case is a field worker or hired labour liable to frequent displacement seasonal labor and imported malaria is a

8) complex problem nearly every where.

9) Border malaria. This calls in my opinion for an urgent regulation which I beg the WHO to take into consideration at the levels concerned.

10) Carelessness as there is no more malaria. Indifference or opposition to drugs mostly for childrens. And very often incapability due to lack of minimum education to take the supplied drug on dosis and times recommanded or prescribed.

Distrut for a drug given freely.

11) Among many others which I escape I want to mention the administrative and financial problems, delays uncooperative attitude still noted after so many years due to lack of understanding the emergencies of any antivector campaign.

I will close the enumeration and in the way of summary may I say: that the difficulties or problems mentioned above, in a sketchy way, form the pattern of problems that can be met among many others, in lesser or greater magnitude, in the course of malaria eradication or any major public health action. Some of them may present an easy solution, but what remains to be stressed is the need to provide for the people of these countries better and greater education facilities, which they lack, and is the ultimate way towards a more progressive and healthies living. May I also take opportunity here to thank beside the WHO the various international agencies mainly UNICEF, who have supported and helped materially or in an advisory way in the realisation of our malaria program.

GENERAL DISCUSSION

Dr. **Paul F. Russell** (U. S. A.) — As Chairman of the Malaria Division of these Congresses, I would thank, in this closing meetings, the section and session officers and all who have participated in the deliberations, for their hearty cooperation and interesting contributions. We all agree, I am sure, that the papers and films have been excellent. Particularly impressive have been the reports on malaria eradication. Certainly, no subject in tropical medicine today has greater interest. We are pleased that the Laveran award took cognizance of this fact and that the Prize was given to Doctor Pampana whose indefatigable labours throughout the world as head of the W. H. O. Malaria Section and Division have constituted such a powerful factor in the remarkable acceleration of malaria eradication during recent years. Speaker after speaker has reported significant progress in his country in the mastery of malaria. Several nations that a few years ago experienced millions of cases of malaria each year had only a few hundred, sometimes less than a score of cases in 1957. Obviously, a good start has been made towards malaria eradication.

But our deliberations have also dealt with problems, particularly as regards vector resistence to insecticides, vector out-door feeding and resting behaviour, and some inadequacies of antimalarial drugs. I would emphasize strongly, as have other speakers, the vital need for expanding basic research in malaria. It is gratifying that countries like Italy, U. K., U. S. A., and others, in which malaria has only very low incidence, are nevertheless supporting malaria research. We hope they, and other countries, will continue to do so on an increasing scale until malaria ceases to be a world menace.

Then, too, there is alwoys the need for money to provide suitable budgets. We are all grateful to W. H. O., P. A. S. O., U. N. I. C. E. F., I. C. A., and local governments for vital assistance without which malaria eradication could still be a dream instead of an operating project in so many countries. I am sure that we will all do what we can to persuade our governments to budjet adequately for malaria eradication and to make generous contributions to the W. H. O. Malaria Eradication Special Account.

Finally, it seems to me that the papers we have heard here during the past few days have indicated clearly that malaria eradication is indeed practicable!

Dr. M. HOLSTEIN (France) — 1) Je désire attirer l'attention du Dr. Mouchet sur le remarquable, mais trop bref, exposé du Dr. Bruce Chwatt sur les campagnes effectuées en Nigeria du Nord.

2) Je ne pense pas que l'exemple du Camerouns puisse donner une indication sur les possibilités d'éradication du paludisme en autres régions d'Afrique: au Cameroun *A. gambiae* n'est pas le vecteur principal alors que dans le reste de l'Afrique c'est fortement la biologie de *A. gambiae* (et en particulier la résistance à certains insecticides) qui cause en grande partie le délai apporté à l'éradication.

3) Je désirerais connaître la raison pour laquelle le Cameroun est passé du D. D. T. à la Dieldrine et ceci sans raison apparente.

Dr. N. SWELLENGREBEL (Netherlands) — Speaker makes the following point.

If resistance of anopheles to insecticides is due to selection of preexisting resistant races it is, obviously, of great importance to reduce to a minimum the chances of selection by reducing to a minimum the portion of the Anopheline population exposed to the effect of the insecticides.

That is being done in my country, where *Selective Spraying* is practiced, that is spraying of only those houses where infected anopheles actually occur. This practice reduces the proportion of anopheles actually exposed to less than one per cent., of the total anopheline population, which, obviously, greatly decreases the chance of a preexisting resistant races being allowed to get the upper hand.

Dr. E. WEEKS (Canada) — Appreciation of encouraging reports on progress of eradication program.

1) Refer to definition of malaria eradication by National Malaria Society mentioned by Dr. Andrews — Definition of Malaria eradication by W. H. O. Expert Committee on Malaria (6th Repart) based on Dep. Nat. Mal. Soc. Thus one single concept.

2) International implications of malaria eradication. Need for intercountry agreements. Role of W. H. O. in stimulating intercountry cooperation and collaboration through conferences, etc.

Dr. M. MEIRA (Portugal) — Mr. le docteur Bustamante; j'ai écouté votre trés intérressante communication à ce Congrès sur le programme, d'éradication du paludisme au Brésil, dont l'ancien «Serviço Nacional» j'ai visité il y a quelques ans.

Je vous félicite par vos succès, et je vous prie, dans votre prochain retour au Brésil, de présenter a Mr. le docteur Pinotti mes plus respectueux hommages.

Mr. le docteur Mouchet: vous avez dit, avant la lecture de votre si intéressante communication, que vous n'avez par écouté dans cette section aucun travail sur l'éradication du paludisme dans l'Afrique Continentale... En fait, je crois que votre communication, et aussi la mienne — sur l'erradication de la maladie obtenue par nous dans l'île de S. Vicente, archipel du Cap Vert, et presentée ici hier — sont les deux seules qui figurent dans le programme de ce Congrès sur ce problème en Afrique.

Dr. J. HAMON (France) — Mon exposé il y a 2 jours a été fait sur un sujet très général, aussi je voudrais insister dans cette séance finale, puisque personne ne semble le faire, sur l'aide considérable qui est apportée, particulièrement aux entomologistes, en Afrique, et probablement dans d'autres régions du Monde, par l'aide de l'O. M. S., notamment par la fourniture de matériel standardisé pour les tests de sensibilité aux insecticides et par son service d'identification du sang ingéré par les moustiques. Il est certain que beaucoup des progrès que nous avons realisés ces dernières années n'auraient pas pu être realisés sans cette aide à laquelle je rends hommage.

PAPERS OFFERED AS FREE COMMUNICATIONS BUT NOT DISCUSSED DUE TO THE ABSENCE OF THE AUTHORS

ERRADICAÇÃO DO PALUDISMO NA VELHA CIDADE DE GOA

Luís José Brás de Sá

INTRODUÇÃO

O paludismo representava na Velha Cidade, desde o passado distante, um problema grave de saúde pública.

Estudos feitos em 1933 demonstraram que os índices esplénico e parasitário eram, respectivamente, de 60 % e 53 %. Em 1948, os referidos índices, esplénico e parasitário, observados, por falta de crianças naturais de Velha Cidade, apenas em 8 crianças, que tinham aí permanência, pelo menos, de um ano e meio, foram, respectivamente, de 62,5 % e 50 %.

Numerosos poços no estado de abandono, em que jaziam pelo despovoamento da cidade, constituíam criadouros do vector principal *A. fluviatilis*.

A população em 1948 resumia-se a 90 habitantes.

Em Junho do referido ano deu-se início à campanha antimalárica.

A realização desta campanha justificava-se, não só porque a Velha Cidade era uma área hiperendémica no meio de aldeias saudáveis, mas também pela sua importância histórica e religiosa, pois ela representa a antiga capital do império português do Oriente e um centro de peregrinação, por ser o repositório do venerando corpo de S. Francisco Xavier.

No trabalho «Combate ao sezonismo na Velha Cidade de Goa», apresentado ao I Congresso Nacional de Medicina Tropical, celebrado em Lisboa de 24 a 29 de Abril de 1952, foram descritos os elementos climáticos, dados epidemiológicos, criadouros de *Anopheles,* a biologia dos anofelinos encontrados e a profilaxia efectuada.

Daremos no presente trabalho uma breve descrição dos processos empregados no referido combate, que foi levado a efeito com êxito e que

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 716-725, 1959

durou desde Junho de 1948 a Dezembro de 1950, e a seguir relataremos o prosseguimento da luta no sentido da consolidação dos resultados obtidos e erradicação do paludismo.

I

Luta antilarvar — Dada a dificuldade de tratamento com D. D. T. de vastos templos, vários corredores e salas, onde existem valiosas obras de arte, e por ser bem conhecida a localização dos criadouros de *Anopheles*, a luta foi fundamentalmente antilarvar.

Fez-se pelo emprego das medidas: *permanente*, como a eliminação de poços abandonados, tendo sido entupidos 897; *temporárias* — verdificação ou aplicação da emulsão de D. D. T. a 2 % nos referidos poços, enquanto não fossem entupidos, e nos caboucos, arrozais, valas de irrigação e ribeiro de Banguenim, sendo os charcos tratados pelo verde-de-Paris em suspensão em óleo pesado; e *biológica* — pelo povoamento de 4 poços e 2 tanques com peixes larvífagos dos géneros *Polyacantus* e *Haplochilus*.

Como complemento da luta, foi feita a luta antimosquito. Foi também posto em prática o tratamento supressivo pela paludrina.

Luta antimosquito — Os conventos e as dependências de igrejas, segundo as possibilidades, as casas, os currais e as ruínas com cobertura, foram tratados interiormente pela emulsão de D. D. T. a 5 %. Na primeira fase da campanha, as pulverizações com D. D. T. foram feitas com intervalos de 5 a 6 semanas, as quais, segundo as instruções do Prof. Cambournac, que visitou a Velha Cidade em 1949, passaram a ser mais espaçadas e de modo que distribuíssem 2 g de D. D. T. por metro quadrado, obtendo-se resultados muito satisfatórios.

Tratamento supressivo — Todos os habitantes foram tratados com paludrina, primeiramente na dose de 100 mg, duas vezes por semana, e depois em dose semanal de 3 comprimidos (30 cg) tomados de uma só vez.

Resultados — Nenhum espécime adulto ou larvar de *A. fluviatilis* foi capturado desde Setembro de 1948.

Os índices esplénico e parasitário foram nulos em Dezembro de 1949.

O tratamento supressivo pela paludrina foi suspenso em Dezembro de 1950.

Não houve casos novos de sezonismo desde 1949.

II

Com o fim de consolidar os resultados obtidos e vigiar a área tratada, foi criado em 1951 um posto anti-sezonático, que se compõe do seguinte pessoal:

1 médico superintendente;
1 enfermeiro;
1 servente e 1 operário eventual.

Este posto tem por funções:

— Vigiar e tratar as águas dos criadouros averiguados ou virtuais.
— Pesquisar semanalmente larvas e *Anopheles* no estado adulto.
— Identificar as espécies anofelinas que apareçam.
— Realizar a aplicação domiciliária de D. D. T. na área da cidade e na zona de protecção em volta da cidade, durante o tempo que se julgar conveniente.
— Tratar doentes que, porventura, apareçam com paludismo.

Luta antilarvar — Continuou a luta antilarvar por meio de D. D. T. nas colecções de água formadas na estação de chuva e noutras conservadas para fins agrícolas.

Luta antimosquito — Fizeram-se, como medida de prevenção, aplicações domiciliárias da emulsão de D. D. T. a 5 % na área da cidade e na zona de protecção de cerca de 2 km em volta da cidade, sendo três as aplicações em 1951, três em 1952 e duas em cada um dos anos de 1953 a 1955. Na zona de protecção foram feitas também aplicações anuais de D. D. T., uma em 1956 e uma em 1957.

Capturas — Foi feita a captura de mosquitos adultos, semanalmente, em 10 estações, durante 15 minutos e sempre por dois empregados do posto.

Foram apanhados raros exemplares da espécie não vectora e frequente em Goa, *A. subpictus*, até 1953, como consta do quadro 1.

Esta espécie desapareceu antes que revelasse resistência ao D. D. T., já observada na aldeia Jwalaheri de Delhi, sujeita às pulverizações com D. D. T. desde 1947. A eliminação dos principais criadouros — cascas de coco, que retinham água das chuvas, e charcos de águas domésticas — deve ter contribuído para o seu desaparecimento.

Desde 1956, o comportamento do posto tem sido passivo, de vigilância rigorosa na área da cidade, fazendo-se pesquisas semanais de larvas e *Anopheles* no estado adulto.

Quadro 1 — *Captura de* Anopheles *na Velha Cidade*

Anos	Número e espécies encontradas
1951	2 *A. subpictus*
1952	1 *A. subpictus*
1953	1 *A. subpictus*
1954	—
1955	—
1956	—
1957	—

RESULTADOS FINAIS

Desde Setembro de 1948, a espécie vectora *A. fluviatilis* deixou de aparecer, quer sob forma larvar quer sob forma adulta, na Velha Cidade. Outras espécies anofelinas também desapareceram.

Os índices esplénico e parasitário, nulos em Dezembro de 1949, e observados anualmente até 1953, continuaram negativos.

Não houve casos novos de sezonismo desde 1949.

A vinda de companhias expedicionárias e algumas famílias com crianças, subindo a população actual a mais de um milhar — factor populacional a considerar em relação à epidemiologia do paludismo —, nenhuma influência exerceu na disseminação da morbilidade por esta doença.

Nas multidões que, durante a exposição do corpo de S. Francisco Xavier, em 1952, permaneceram na Velha Cidade muitos dias, nenhum casos averiguado de paludismo local se registou.

CONCLUSÃO

Os resultados obtidos — desaparecimento do sezonismo, do seu vector e de outras espécies anofelinas, há mais de três anos —, permitem-nos concluir que o paludismo foi erradicado da Velha Cidade.

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A EVOLUÇÃO DA AMALÁRIA NA ÍNDIA PORTUGUESA

Luís José Brás de Sá

I — *Antes da organização das brigadas sanitárias contra a malária*

A Índia Portuguesa compreende três distritos: Goa, na costa do Malabar, Damão, na costa do golfo de Cambaia e Dio, na costa do Guzerate.

Em Goa, a endemia malárica é muito leve ou nula nos concelhos de Goa, Bardez, Salcete e Mormugão, que constituem a parte do território denominada *Velhas Conquistas*, enquanto se torna elevada na parte denomiada *Novas Conquistas*.

Havia excepção a esta regra geral. No concelho de Goa existe uma localidade, antiga capital do império português do Oriente, Velha Goa, onde o paludismo era hiperendémico.

Em Dio e Damão a malária existe em intensidade média em diferentes partes, sendo hiperendémica no concelho de Praganã.

O quadro seguinte indica os diversos graus da endemia malárica, conforme a planta topográfica da malária, que fora organizada em 1918 e 1929.

Número de aldeias impaludadas e os seus índices esplénicos

Concelhos	0-10 %	11-20 %	21-30 %	31-40 %	41-50 %	51 a 100 %
Satari	18	5	14	5	2	8
Sanquelim	3	12	6	4	0	0
Sanguém	0	5	3	9	2	19
Canácona [1]	41	15	13	14	11	19
Quepém	5	16	9	2	1	10
Damão	1	—	6	10	5	3
Praganã	0	0	0	0	0	69
Diu	0	1	4	1	1	0

[1] O índice esplénico foi determinado segundo os bairros.

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 716-725, 1959

Na Velha Goa, como resultado dos primeiros estudos feitos em 1933, foram encontrados os índices esplénico e parasitário, respectivamente, de 60 % e 53 %. Numerosos poços, no estado de abandono em que jaziam por virtude do despovoamento da cidade, constituíam criadouros do vector principal *A. fluviatilis*.

Nessa época, a população se resumia a 75 almas, das quais 28 sacerdotes. Todos referiam histórias clínicas das sezões. O terror do sezonismo fazia que a maioria da população passasse as noites fora da cidade, nas aldeias próximas, Ribandar, Piedade e Corlim, onde a endemia não existia ou era leve (índice esplénico de 3 %).

As espécies anofelinas identificadas na Velha Cidade, na fase larvar e no estado adulto, foram:

Na estação seca e quente: *A. fluviatilis, A. barbirostris, A. jamesii, A. vagus* e *A. subpictus*. Nas estações pluviosa e seca e fresca, além das referidas espécies, *A. varuna, A. minimus* e *A. hyrcanus* var. *nigerrimus*.

O vector da malária em Sanguém e Canácona é o *A. fluviatilis*.

Outras espécies anofelinas encontradas nas Novas Conquistas, segundo as pesquisas feitas de 1917 a 1929, foram: *A. rossi* (=*A. subpictus*), *A. ludlowi* (= *A. sundaicus*), *A. jamesii, A. fuliginosus* (=*A. annularis*), *A. barbirostris, A. culifacies, A. leucosphyrus, A. maculatus, A. sinensis* (=*A. hyrcanus*), *A. culiciformis, A. aitkeni* e *A. karwari*.

Em 1932 se fundara a campanha antimalárica nas *Novas Conquistas*, onde, sob o programa geral de *Fomento das Novas Conquistas*, o assunto foi encarado no concelho de Sanguém sob prismas vários: estradas e vias de comunicação dos centros mais afastados à sede, abastecimento da água potável e saneamento antimalárico, pela formação de 4 núcleos sanitários a cargo de médicos e 5 subnúcleos a cargo de enfermeiros, munidos de ambulâncias para o tratamento profiláctico de todos os habitantes das aldeias com o índice esplénico de mais de 50 %, compreendendo uma plasmoquinação primária (0,02 plasmoquina + 0,5 sulf. q. por dia) durante oito dias, seguida de tratamento complementar de uma dose semanal *ut supra* durante doze semanas. Os habitantes das localidades com índice esplénico entre 31 a 49 % recebiam apenas o tratamento primário.

Foram tratados com verde-de-Paris os locais da criação de larvas anofelinas dentro e à volta das povoações.

Decorridos, porém, poucos anos, os trabalhos ficaram suspensos e a malária continuou a grassar com intensidade, após pequena pausa.

II — *Depois da organização das brigadas sanitárias*

A organização antimalárica funciona sob a orientação superior do director dos Serviços de Saúde.

Compreende equipas campestres, compostas de 1 a 3 enfermeiros e alguns trabalhadores rurais. Cada unidade trabalha sob a fiscalização de um delegado de saúde, especializado em malariologia. O director dos Serviços de Saúde superintende nos trabalhos e fixa os planos futuros, que consistem em estender gradualmente a campanha para toda a área palustre de Goa, Damão e Dio.

COMO SE REALIZOU O COMBATE À MALÁRIA NA VELHA CIDADE

Em Junho de 1948 teve início o programa de profilaxia da malária na Velha Cidade.

A prospecção feita no início da campanha indicou 62,5 % de índice esplénico e 50 % de índice parasitário.

Pessoal empregado: 1 delegado de saúde, treinado em malariologia e, para trabalhos de campo, 2 capatazes e 8 operários.

Profilaxia — Dada a dificuldade de tratamento com D. D. T. do interior dos edifícios na Velha Cidade, onde existem templos de grandes dimensões e com obras de arte muito valiosas nas suas paredes, a base da luta foi a luta antilarvar pelo entupimento de 897 poços abandonados, emprego dos larvicidas — emulsão de D. D. T. a 2 % ou verde-de-Paris — nas referidas colecções de água, enquanto não fossem entupidas, e noutras, como caboucos, valas de irrigação, arrozais e ribeiro de Banguenim, sendo os charcos tratados pelo verde-de-Paris em suspensão em óleo pesado e povoamento de alguns poços e tanques com peixes larvívoros dos géneros *Polyacanthus* e *Haplochilus*.

Como complemento de maior valia, foi empregada, segundo as possibilidades dos edifícios, interiormente, a emulsão de D. D. T. a 5 %, em intervalos espaçados e de modo a distribuir 2 g de D. D. T. por metro quadrado. Foram também postos em prática o tratamento supressivo pela paludrina e o tratamento de doentes.

Resultados — Nenhum espécime adulto ou larvar de *A. fluviatilis, varuna* e *minimus* foi capturado desde Setembro de 1948.

O índice esplénico, que baixara a 12,5 % em Dezembro de 1948, isto é, no fim do período habitual de maior intensidade de transmissão, foi nulo em Dezembro de 1949, bem assim o índice parasitário.

O tratamento supressivo pela paludrina foi suspenso após 2 anos e meio, por desnecessário.

Não houve registo de casos novos de malária desde 1949.

Com o fim de consolidar os resultados obtidos e erradicar o paludismo, foi criado em 1951 um posto anti-sezonático, que se compõe do seguinte pessoal:

1 médico superintendente;
1 enfermeiro;
1 servente e 1 operário eventual.

Este posto tem por funções:

— Vigiar e tratar as águas dos criadouros virtuais na Velha Cidade.
— Pesquisar larvas e *Anopheles* no estado adulto.
— Identificar as espécies anofelinas que apareçam.
— Realizar a aplicação domiciliária de D. D. T. na área da cidade e na zona de protecção em volta da cidade, durante o tempo que se julgar conveniente.
— Tratar doentes que, porventura, apareçam com paludismo.

Desde 1956 o comportamento do posto tem sido passivo de vigilância rigorosa na área da cidade.

O vector *A. fluviatilis* não mais voltou a aparecer. Outras espécies anofelinas também desapareceram.

Os índices esplénico e parasitário continuaram negativos.

Na população, que já sobe a mais de um milhar, e nas multidões que, durante a exposição do corpo de S. Francisco Xavier, em 1952, permaneceram muitos dias na Velha Cidade, nenhum caso de paludismo local foi averiguado.

Dos resultados encontrados pode concluir-se que o paludismo foi erradicado da Velha Cidade.

Em 1950 começaram as operações de combate à malária em Sanguém e Canácona.

O método adoptado foi a aplicação residual de D. D. T. às paredes internas das casas até à altura de 3 m do pavimento e aos tectos baixos.

O quadro seguinte indica a considerável redução na incidência da malária:

	Ano	Índice esplénico	Índice parasitário
Sanguém	1950	33 %	4,5 % (*a*)
	1951	9 %	1 %
	1952	5 %	(*b*)
	1953	2,5 %	(*b*)
Canácona	1950	35 %	5 % (*a*)
	1951	9 %	1 %
	1952	4 %	(*b*)
	1953	0 %	(*b*)

(*a*) A prospecção foi feita fora do período de transmissão, que vai de Dezembro a Junho.

(*b*) Menos de 1 %.

Pode, pois, dizer-se que as áreas protegidas, que eram as mais insalubres das Novas Conquistas, são hoje as mais salubres.

No concelho de Praganã as operações de combate à malária foram iniciadas em 1953 e protegeram 18 000 habitantes.

SETE ANOS DE CAMPANHA ANTIMALÁRICA EM SAGUÉM

Dr. Pondorinata A. S. Borcar

I — INTRODUÇÃO

A área da Delegacia de Saúde de Sanguém fica situada ao longo da cordilheira dos Gates Ocidentais, numa faixa de 10 a 20 quilómetros de largura a oeste da cordilheira; o solo é irregularmente acidentado e sulcado por ribeiros e nascentes; em certas regiões, na base da cordilheira, existem infiltrações de água formando lodaçais e alagoas com vegetação nas margens e à superfície. Certos cursos de água são aproveitados, durante a época seca, para os fins da cultura de arroz e cana sacarina, desviando as suas águas por meio de represas e pequenos canais de irrigação. Todos esses locais constituem os principais focos da criação do *A. fluviatilis*, vector da região.

Exceptuados os campos aproveitados para a cultura, o resto é coberto por uma vegetação arbustiva e subarbustiva exuberante e ainda densos matos.

A área controlada da Delegacia tem a superfície aproximada de 415 km² e população de 15 000 habitantes, que vive dispersa, na sua maioria, em casinhas e choupanas, formando povoações distantes umas das outras. Além desta população fixa, vivem nesta área 10 a 15 mil trabalhadores das minas, vindos de outras regiões, umas sadias e outras maláricas, os quais residem em barracas abertas e completamente desprotegidas. A zona da exploração mineira fica quase toda na área da alta incidência malárica.

O clima de Goa é dominado pela monção do Índico e temos pràticamente duas estações, uma de chuva, de Junho a Outubro, e outra seca, de Novembro a Maio. A temperatura e a humidade relativa são favoráveis, durante todo o ano, ao desenvolvimento dos mosquitos e dos parasitas no organismo dos vectores. Sucede, porém, que na época pluviosa a enorme precipitação das águas e as correntes caudalosas dificultam a vida das larvas e de mosquitos adultos, não havendo pràticamente transmissão de malária nessa época.

II — INVESTIGAÇÃO PRELIMINAR

Do exame das crianças apurou-se o índice esplénico de 15 % para toda a área. As freguesias altamente endémicas, Bati, Curdi e Netorlim, tiveram respectivamente 53 %, 31 % e 26 % de índice esplénico e 5 %, 4 % e 4 % de índice parasitário (quadro 1)

QUADRO 1

Freguesias	Número de crianças examinadas	Número de crianças com baço hipertrofiado	Índice esplénico	Índice parasitário
Bati	77	41	53,2 %	5 %
Curdi	176	54	30,7 %	4 %
Netorlim	161	41	25,5 %	4 %
Quirlapale	353	24	6,8 %	(*a*)
Sanguém	366	11	3,5 %	(*a*)

(*a*) Não foi estudado o índice parasitário por ser fraca a intensidade da endemia.

Dos hematozoários, as espécies dominantes foram o *P. falciparum* e *P. vivax*, tendo sido raro o *P. malariae*.

Foram identificadas 13 espécies de *Anopheles: A. aconitus, A. annullaris, A. barbirostris, A. fluviatilis, A. hyrcanus, A. jamesi, A. karwari, A. minimus, A. phillipinensis, A. subpictus, A. tessellatus, A. vagus* e *A. varuna.*

Verificou-se que o vector da região era o *A. fluviatilis,* como também indicam os estudos anteriores do Prof. Froilano de Melo e Dr. Brás de Sá.

Este mosquito cria-se:

a) Nas margens dos rios de água doce, ribeiros e nascentes de cursos lentos e margens irregulares e revestidas de palha e vegetação.

b) Pequenos canais de irrigação.

c) Charcos e alagoas resultantes da infiltração das águas nas bases das montanhas.

Os mosquitos adultos entram nas casas de habitação durante a noite, de preferência antes da meia-noite, permanecem nas paredes e tectos após a sua refeição de sangue e saem nos dias subsequentes, quer à procura dos abrigos de dia quer para os fins da oviposição.

III — MEDIDAS ANTIMALÁRICAS

Como a área controlada fosse essencialmente rural, com as suas inúmeras e extensas colecções aquáticas, algumas de difícil acesso, e considerando os hábitos da população, que vive dispersa e, portanto, incontrolável, pusemos de parte a chemoprofilaxia sistemática e a luta antilarvar, medidas que seriam de execução e fiscalização difíceis, além de antieconómicas; e adoptámos, como base da nossa campanha, a luta contra o mosquito adulto por meio das aplicações de D. D. T. Este método era de realização e fiscalização fáceis, seguro, económico e de eficácia já provada nas áreas rurais dos países do sudeste da Ásia.

O D. D. T. foi empregado sob a fórmula da emulsão a 5 % e aplicado por meio das bombas do tipo *stirrup pumps*.

Foram tratadas com o insecticida todas as casas habitadas e desabitadas, currais, barracas e ruínas.

O D. D. T. aplicado na dose anual de quatro gramas por metro quadrado, dividida em quatro aplicações com intervalos de dois meses, durante o período de Outubro-Maio. Após cinco anos, foi reduzida a dose a dois gramas, dividida em duas aplicações, com intervalo de quatro meses, ampliando o *contrôle* a povoações com índices esplénicos inferiores a 10 %.

A administração das drogas limitou-se a casos clínicos e crianças que durante a investigação apresentavam baço hipertrofiado ou parasitas no sangue. Nas explorações mineiras foi recomendado administrar aos trabalhadores uma dose semanal de três decigramas de paludrina, no primeiro ano da campanha.

IV — RESULTADOS OBTIDOS

Logo após as primeiras aplicações de D. D. T., fizeram-se sentir os efeitos, tendo-se verificado uma melhoria geral na saúde da população defendida, com a redução de malária e de outras doenças transmitidas pelos insectos, como diarreias, desinterias, gastrenterites infantis, febres entéricas, etc.

Para a melhor apreciação do estado da endemia procedemos ao estudo dos índices esplénicos e parasitários da população fixa das freguesias altamente endémicas. Os resultados apurados comparam-se muito favoràvelmente com a incidência inicial e indicam uma baixa considerável após três anos (2 a 3 %, em vez de 26 a 53 %), tendo esta baixa consolidado nos anos ulteriores (quadro 2).

QUADRO 2

Freguesias	Anos	Número de crianças examinadas	Número de crianças com baço hipertrofiado	Índice esplénico	Índice parasitário
Bati	1950	77	41	53,2 %	5 %
	1951	106	10	9,4 %	1 %
	1952	109	7	6,4 %	
	1953	138	4	2,9 %	
	1955	139	4	2,9 %	
	1957	158	3	1,9 %	
Netorlim	1950	161	41	25,5 %	4 %
	1951	139	14	10,1 %	1,5 %
	1952	176	9	5,1 %	
	1953	182	4	2,2 %	
	1955	194	4	2,1 %	
	1957	247	5	2,0 %	
Curdi	1950	176	54	30,7 %	4 %
	1951	210	17	8,1 %	0,5 %
	1952	264	14	5,3 %	
	1953	365	9	2,5 %	
	1955	289	4	1,4 %	
	1957	324	3	0,9 %	

A indústria mineira lucrou muito com a campanha, o que concorreu para o progresso da economia do País. Não obstante as concessões mineiras estarem quase todas situadas na área altamente endémica, a incidência da doença entre os trabalhadores foi muito reduzida ainda nos primeiros anos da campanha e é hoje pràticamente nula. O saneamento das áreas fortemente insalubres de outrora constitui uma garantia segura para a principal indústria do Estado da Índia, quando no passado as empresas agrícolo-industriais falhavam com a debandada dos trabalhadores, motivada ùnicamente pelo paludismo.

Entre os funcionários europeus que servem neste concelho, em diferentes serviços que os obrigam a percorrer regiões matosas de dia e de noite, não consta ter sido registado um único caso de malária, quando é sabida a susceptibilidade do europeu, vindo às regiões tropicais, em contrair a malária, que nele se manifesta com maior gravidade do que nos naturais. É de se notar que esses funcionários não estão protegidos com quaisquer medidas de protecção individual nem lhes são administradas drogas preventivas. É esta uma prova das mais eloquentes de que a transmissão da malária, nesta área, está já cortada.

A influência da campanha também se fez sentir nos elementos demográficos, não obstante esses elementos terem sido prejudicados pelo desenvolvimento da indústria mineira, tendo registado no quinquénio 1951-1955 muitos óbitos por acidentes de trabalho e da viação (quadro 3).

QUADRO 3

	Nascimentos	Óbitos	Aumento da população	Percentagem do aumento da população
Média de cinco anos (1946 a 1950)	403	193	210	1,55 %
Média de cinco anos (1951 a 1955)	483	235	248	1,84 %

V — CONSIDERAÇÕES FINAIS

A área controlada teve a velha reputação de ser a mais insalubre do distrito de Goa, a causa desta insalubridade era a secular endemia malárica.

A presente campanha conseguiu reduzir a doença a tal ponto que, após três anos de trabalho, a malária deixou de ser, pràticamente, o problema de saúde pública da região, melhoria que se consolidou nos anos ulteriores.

Há que considerar, porém, que a campanha não atingiu ainda a fase da erradicação, porquanto se registam casos, embora raros, sobretudo nas regiões mineiras da raia. As capturas insistentes também conseguem descobrir espécimes do *A. fluviatilis*.

Três circunstâncias concorrem para esta incidência:

a) Residências dos trabalhadores das minais em barracas abertas, algumas das quais surgem depois de as brigadas procederem às aplicações do insecticida e, por consequência, não possuem a protecção necessária.
b) Vizinhança de áreas, embora de endemia moderada, onde as medidas antimaláricas não têm sido adoptadas com o mesmo rigor.
c) Introdução na área controlada dos trabalhadores das minas portadores da infecção malárica.

A existência de indivíduos portadores de parasitas, do vector e dos locais da sua criação, indicam a necessidade de continuarmos a campanha, a qual, para atingir a erradicação, terá de se estender a outros concelhos de Goa, embora de endemia moderada, além duma vigilância cuidadosa quanto às circunstâncias das alíneas *a*) e *c*).

LAS 4-AMINOQUINOLEINAS EN LA ERRADICACION DEL PALUDISMO — VALORACION EPIDEMIOLOGICA DE UNA Y DOS DOSIS DE 600 MILIGRAMOS DE CAMOQUIN

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La participación creciente de los medicamentos en las campañas de erradicación del paludismo, ha reactualizado un método de lucha que, en los años coincidentes con el periodo hiperbólico de los insecticidas habia sido relegado a un plano inferior. La inmensa mayoria de los paludologoa están hoy convencidos del importante papel que a la quimioterapia le está reservado en el futuro de la metodologia erradicante y de la paridad de esta técnica con la de los insecticidas en su planificación.

Bueno será sin embargo recordar a este rsepecto, aunque solo fuera por lo que tiene de satisfacción intima para el Autor las palabras inciales de un trabajo publicado por Lozano Morales en 1951 en relación con las pautas de ataque de cloroquina: «...la supresión del ataque agudo de paludismocon su doble finalidad profiláctica y terapéutica constituye todavia hoy una realidad inconcuso y una de las técnicas electivas en los programas de lucha contra la enfermidad, debiendo emplearse siempre junto a aquellas otras tendentes a la erradicación de los mosquitos vectores».

Que posibilidades ofrecen los modernos fármacos? Concretándo-nos al cese de la transmisión, objetivo primordial que debe perseguir cualquier método de extirpación del paludismo, el éxito de los medicamentos depende de que proporcionen una cura supresiva al mas alto nivel y de que seempleen con caracter masivo en la región afectada, de donde se desprende la conveniencia de una técnica de administracción sencilla que asegure su ingestión al limite por una enfermeria generalmente propensa al abandono.

En realidad nada ha cambiado en este orden de ideas desde que Lozamo Morales en el trabajo antes citado observava como dentron del objetivo general de hallar un supresivo total la tendencia fué acortar el tiempo de cura sustituyendo las pautas largas por otras de breve duración. Estas premisas no han variado permitiendo a los modernos medicamentos de acción multiplicada y minima toxicidad, alcanzar las ventajas actuales. Cierto que seguimos sin encontrar el fármaco capaz de realizar con seguridad absoluta la esterilización de la carga parasitaria, pero si repasamos siquiera sea someramente el camino recorrido y los resultados logrados, llegaremos a la conclusión de que, practicamente, aquella meta ideal se ha cubierto.

Para Raffaele y Carrescia, la eficacia de algunos modernos medicamentos de síntesis es tal, que pueden asegurar la desaparición de los sintomas y la eliminación del parasitismo de la sangre con una sola dósis de los mismos. Verdad es que la nota publicada ultimamente por estos autores se apoya en una casuística tan exigua y tan alejada del tipo natural de infección que, sus conclusiones, por fuerza deben ser acogidas con ciertas reservas. Mas demostrativas son las experiencias realizadas en los paises orientales y, particularmente, en la India. De ellas se desprenden los satisfactorios resultados obstenidos por J. Singh a base de 400 y 600 miligramos de Resochin y los de Gupta con 600 miligramos de Cloroquina, respondiendo a este tenor las recomendaciones terapúticas contenidas en el Documento de la O. M. S. WHO/Mal//185, relativo a un nuevo plán de erradicación preparado por la Oficina Sanitaria Panamericana y sometido a consulta por la Organización Mundial de la Salud entre los miembros de su cuadro de Expertos en Paludismo.

Un comun denominador para este tipo de curas abreviadas lo constituye la dósis de 600 miligramos cualquiera sea el preparado comercial que se emplee. Gupta advierte que dósis únicas de 1 500 miligramos han producido en sus pacientes accidentes tóxicos. Por el contrario Vila Coro en 107 casos tratados en la Guinea Española esa misma cantidad de Resochin no los observa. Tampoco Lozano Morales los ha tenido en su casuística empleando 1 000 miligramos de Resochin seguidos de otros 1 000 a las seis horas, siempre que la ingestión se hiciera tras las comidas. De todas maneras hay un aspecto en toda esta serie de experiencias que aparentemente no esta tratado con un cuidado especial y es el de la tasa y tipo de recidivas que tales curas abreviadas proporcionan. Es este problema del que fundamentalmente hemos querido ocuparnos por considerar que en la erradicación el caso que plantean las recidivas es muy semejante al derivado de la resistencia de los mosquitos a los insecticidas.

PARTE EXPERIMENTAL — DOSIS UNICA DE 600 MILIGRAMOS DE CAMOQUIN

Entre los meses de Abril y Junio de 1957 hemos tenido ocasión de utilizar esta pauta en la enfermeria del único brote palúdico existente en España en la comarca noroeste de la provincia de Cáceres.

La docificación por edades fué:

Hasta 5 años	200 miligramos
De 6 à 9 años	400 »
De 10 años en adelante	600 »

Después de una vigilancia que se ha prolongado hasta el 30 de Abril de 1958 los resultados fueron:

	Especie plasmodial	Nº de casos	Recidivaron	Porcentaje
Primoinfecciones	*Pl. vivax*	5	1	20
Recidivas	*Pl. vivax*	27	8	29

Desde el punto de vista de la erradicación y en tanto no se cuente con medicamentos supresivos de valor absoluto, sea cual fuere la ubicación del parasitismo en el organismo humano, el control de las recidivas continuará siendo sin duda el método mas apropriado para valorar la utilidad profiláctica de aquellos.

Desde las primeras experiencias de los investigadores alemanes se supo que las 4-aminoquinoleinas no solo estaban casi desprovistas de toxicidad si no que asi mismo poseian un poder parasiticida superior a todas las sustancias conocidas. Estas conclusiones habrian de facilitar bien pronto las pautas de ataque de corta duración, sobre las que Lozano Morales publicó, en 1951 para el Nivaquin y en 1952 para el

Resochínensendos, trabajos, con dosis el primero de 1 800 miligramos en 24 horas y 2 500 miligramos el segundo en 18 horas, con ausencia de recidivas. Verdad es que la ausencia de recidivas no es producto único de la acción de los medicamentos. Efectivamente en numerosos estudios sobre quimioterapia me ha sido dado observar con frecuencia los efectos desiguales de los fármacos frente al *Plasmodium vivax*. Aparentemente los fallos son mas acusados cuando se opera sobre una casuística en fase epidémica y, sobre todo, en el declive del brote agudo. Es entonces cuando junto a cepas parasitarias de fácil eliminación se encuentran otras menos accesibles que podrian justificarse por estar dotadas de un acusado tropismo tisular. Asi tendrian explicación las repetidas recidivas padecidas por ciertos individuos en esa fase del ciclo epidémico, la mayor tasa de recidivas en los enfermos ya recidivantes, los buenos efectos que para la curación de estos y aquellos proporciona la adición a las curas de una 8-aminoquinoleina, etc.

De todas maneras ya en 1945 advertiamos que, para considerar adecuada una pauta teráp̦eútica con criterio epidemiológico, esta deberia evitar la totalidad de las recaidas a corto plazo debidas a la deficiente esterilización del parasitismo hemático, y eliminar o reducir al limite las recidivas tardias de origem tisular cuyo porcentaje podia ser establecido para cada medicamento y posologia.

Asi es evidente que el 28 por ciento de recidivas del bloque que comentamos no puede respaldar favorablemente la dosis unica de 600 miligramosy menos aun si, paralelamente, la comparamos en sus resultados con los habidos en anteriores experiencias. Es cierto que estas recidivas se han producido generalmente a los dos y tres meses lo cual prueba una vez mas el enorme poder parasiticida hemático de la Cloroquina. Sin embargo esto no basta para alterar la regla de la quimioterapia erradicante y, unicamente ante una situación de emergencia podria justificarse tan exigua dosificación en tanto tal situación se mantuviera, para solucionar el grave problema que entraña una enfermeria numerosa y desmoralizada.

DOSIS DE 1 200 MILIGRAMOS EN DOS TOMAS

Buscando un mayor efecto supresivo sin alterar visiblemente la sencillez de la pauta y convencidos de que el organismo asimila y retiene en mayor grado estos medicamentos en ingestión fraccionada, a partir del mes de Junio de 1957 duplicamos la dosis de Camoquin administrándola en dos tomas con un intervalo mínimo de seis horas. Tratamos asi 61 enfermos que posteriormente fueron estrechamente vigilados:

	Especie parasitaria	Nº de casos	Recidivaron	Porcentaje
Primoinfecciones	*Pl. vivax*	33	2	6
Recidivas	*Pl. vivax*	28	3	11

Sin que este resultado pueda calificarse de definitivo la experiencia es prometedora aunque no se hayan alcanzado los efectos concluyentes de la dosis de 1 800 miligramos que es, a nuestro entender la pauta tipo para las 4-aminoquinoleinas.

La respuesta al medicamento de primoinfecciones y recidivas continua cualitativamente acusando el mismo caracter, pero la tasa media de curaciones definitivas encaja ahora bastante mejor en las directrices apuntadas. Por otra parte, esta doble dósis es asi mismo de facil y correcta administración, ya que recomendandose la ingestión de la segunda toma en un momento en que aún persisten los síntomas clínicos, se tiene la seguridad de que el paciente no abandonará el tratamiento. Esta seguridad no puede ser invocada tan categoricamente para las curas en tres dosis espaciadas según se deduce de nuestra propria experiência en la misma región en el año 1956.

CONCLUSIONES

Una sola dosis de 600 miligramos de Camoquin (Cloroquina) ha resultado francamente deficitaria en la enfermeria tratada.

La Cloroquina desarrolla al límite su acción supresiva administrada en dósis de 1 800 miligramos en tres tomas de 600 miligramos con intervalos de seis horas, si bien en tratamientos no vigilados la tercera toma no es ingerida en bastantes ocasiones.

En atención a los factores derivados del tipo de enfermeria puede aceptarse como pauta óptima para las campañas de erradicación la dosis de 1 200 miligramos en dos tomas de 600 miligramos con intervalo de seis horas.

MORALES, A. L.—*Las 4-aminoquinoleinas en la erradicación del paludismo*

RESUMEN

Se estudian en este trabajo los efectos del Camoquín (Cloroquina) en dosis única de 600 miligramos y en dos dosis de 600 miligramos con pausa de seis horas, comparandose los resultados con los de anteriores experiencias en las que utilizaron cantidades de 1.800 miligramos distribuidos en tres tomas.

El autor llama la atención sobre el problema que pueden plantear las recidivas en el curso de los programas de erradicación y la necesidad de evitar estas o reducirlas al mínimo si se desea acelerar el cese de la transmisión y reducir las posibilidades de reinfecciónes, considerando la quimioterapia no como supresivo residual tras el uso de los insecticidas, si no como método erradicante en paridad con aquellos desde el comienzo de las campañas.

Tras expoher sus puntos de vista sobre el complejo terapútico en epidemiología, se alcanza la conclusión de que la dosis de 1.200 miligramos de Camoquin en dos tomas de 600 miligramos con seis horas de intervalo, es la que responde a un mayor criterio científico.

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ERADICATION OF MALARIA IN THE UNION OF SOUTH AFRICA

(Statement)

Dr. B. A. Dormer

Two areas in the Union of South Africa are affected: Natal & Zululand & The Northern Transvaal.

In Natal the extent of the original malarious areas (epidemic and endemic) twenty-five years ago was 20,000 square miles. In the Transvaal this area was 75,000 square miles.

In Natal today control measures are still considered necessary in an area of 7,500 square miles and transmission still occurs in 4,000 square miles.

In the Transvaal control measures are still in force over 22,000 square miles, and in about 13,500 square miles transmission still occurs.

The attached chart gives some idea of the results of control measures in Natal and Zululand.

In the Transvaal the position is reflected in the following table:

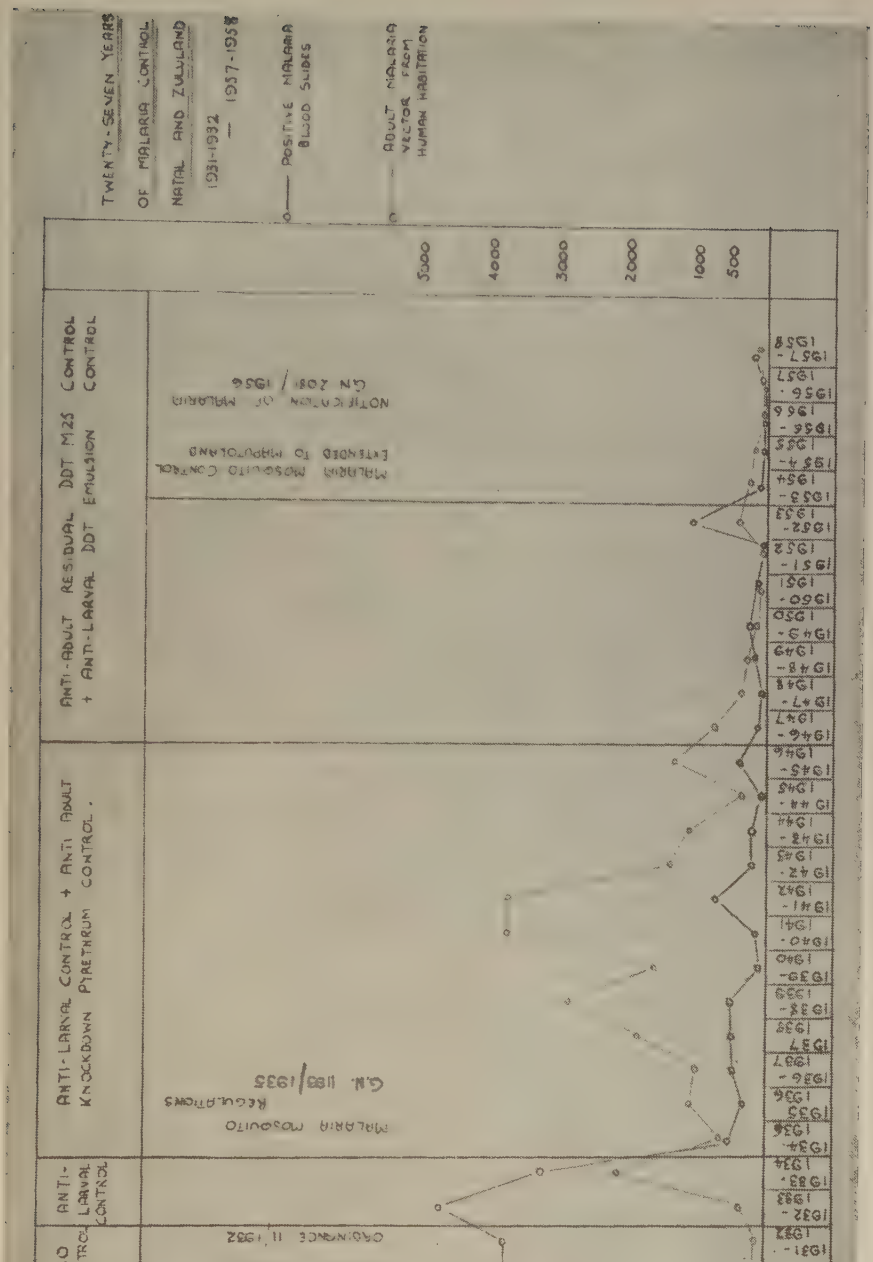
Number of malarial cases in Northern Transvaal

Year ending 30th June	No. of cases
1953	700
1954	104
1955	251
1956	131
1957	92
1958	79

Measures to reduce the incidence of malaria have been in force in the Union of South Africa since 1930.

Since 1946 more intensive control has been effected by using D. D. T. and B. H. C. in extensively planned campaigns, and today it is con-

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 738-740, 1959


TWENTY-SEVEN YEARS
OF MALARIA CONTROL
NATAL AND ZULULAND
1931-1932 — 1957-1958
POSITIVE MALARIA BLOOD SLIDES
ADULT MALARIA VECTOR FROM HUMAN HABITATION
5000
4000
3000
2000
1000
500
NO CONTROL
ANTI-LARVAL CONTROL
ANTI-LARVAL CONTROL + ANTI ADULT KNOCKDOWN PYRETHRUM CONTROL.
ANTI-ADULT RESIDUAL DDT M25 CONTROL + ANTI-LARVAL DDT EMULSION CONTROL
MALARIA COMMITTEES ORDINANCE 11/1932
MALARIA MOSQUITO REGULATIONS G.N. 1183/1935
MALARIA MOSQUITO CONTROL EXTENDED TO MAPUTOLAND
NOTIFICATION OF MALARIA GN 208/1956
1931-1932
1932-1933
1933-1934
1934-1935
1935-1936
1936-1937
1937-1938
1938-1939
1939-1940
1940-1941
1941-1942
1942-1943
1943-1944
1944-1945
1945-1946
1946-1947
1947-1948
1948-1949
1949-1950
1950-1951
1951-1952
1952-1953
1953-1954
1954-1955
1955-1956
1956-1957
1957-1958
5000
4000
3000
2000
1000
500

sidered that well over 80 % of the population at risk ten years ago is now free of malaria.

There is no evidence to date that D. D. T. and/or B. H. C. have lost any effect in controlling the adult or the larve of the vector in South Africa.

Compulsory notification of malaria was introduced in 1956 and the distribution of malaria cases and of parasite carriers discovered by taking a large number of blood smears shows that slight transmission still occurs in certain areas; but the position has been reached when it seems possible that by continuing our present control measures and by introducing chemoprophylaxis and intensive chemotherapy in defined areas final eradication of the disease in South Africa is in sight.

The economic progress of a region in which malaria has been controlled more than repays any money spent for this purpose.

· In one area of the Transvaal for example afforestation of mountain slopes has increased from 42,000 acres in 1940 to 183,700 acres in 1958. In the same period annual citrus production has increased from 1 million to 8.5 million pockets, the area of agricultural land under productive irrigation has increased from 18,000 to 80,000 acres. Production of maize and groundnuts has increased three-fold and of castor oil from nil to 250,000 bags of seed annualy.

This progress is due to the improvemeint of the health of the human community due to malaria control and it appears a reasonable ideal that the close co-operation of good neighbour states will result in complete eradication of malaria in the whole of Southern Africa.

THE ROLE OF DRUGS IN MALARIA ERADICATION IN SOUTH EAST ASIA

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The Second Asian Malaria Conference (1956), stated that the ultimate aim of nation-wide malaria control programmes must be eradication of the disease. At that time it was considered that the chief place of antimalarial drugs was to eradicate infections already present when spraying programmes were initiated although they were accepted as useful also in epidemic malaria and in the suppression of malaria in pioneer settlers and in those people whose occupations kept them out--of-doors at night. It is interesting that the conference recorded an opinion that while the theoretical possibilities were good, yet practical difficulties confronted their use and particularly so in suppression.

During the subsequent three years the increase in seriousness of insecticide resistance has influenced national malaria control policies by an awareness that there might be a time limit on the effective use of insecticides and it was almost inevitable that eradication should become the objective. Any means that may reinforce residual insecticides in bringing it nearer attainment must be, therefore, examined for their usefulness, for no man ànows how much time remains.

This paper attempts an assessment of the role of drugs in malaria eradication but does not discuss their pharmacological properties nor their dose regimes, these having been adequately described by Covell *et al.* (1955), Macdonald (1957) and in the Technical Report Series of the World Health Organization (1954, 1957). Emphasis will be chiefly on those aspects that concern the field worker, finding the cases and ensuring that the required number of tablets are taken.

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In broad grouping, antimalarial drugs may be of special use in the following situations:

(i) Residual insecticides alone may be too slow in reducing an initial high incidence of malaria, or else satisfactory progress may be halted before complete interruption is achieved.

(ii) In India and other large countries an eradication programme may not necessarily start simultaneously in every province. Drugs then may be useful as supportive measures to help late starting areas to catch up to the general level.

(iii) Drugs may have an unique place in the eradication of malaria in certain population groups whose lives, as so graphically described in a WHO Technical Report (1956), «are not normally led within four walls which can be treated with residual insecticides». These people may be fishermen or farm and forest workers or they may be nomads whose tents, so often pitched, struck and packed, possess «walls» that are not at all suitable for treatment with insecticides apart from the difficulties of finding the encampments in lonely trackless deserts.

(iv) There may be groups, perhaps several hundreds of thousands in number, still living a tribal existance in remote and inaccessible mountains that cannot be reached by spraying teams.

(v) The usefulness of drugs in checking epidemics is so obvious as to require no further discussion.

(vi) In the modern concept of malaria eradication, drugs assume the leading role.

(vii) There remain the urgent demands which may be made on drugs should malaria transmission no longer be controllable because of vector resistance to residual insecticides.

DRUGS IN RELATION TO SPECIAL SITUATIONS

The ideal qualities of an antimalarial drug have been given by Bruce-Chwatt (1956). This list specifies virtues of causal prophylaxis, suppression, rapid and complete curative action, sporontocidal effect, impossibility of creating parasite resistance, together with low toxicity, very slow excretion, palatability and low cost.

To meet most of the situations listed in this paper the requirements may be set rather lower. Were there a drug that, while cheap and non-toxic, was also an efficient sporontocide and whose effect was so long-lasting that one — at the most, two — administrations would last throughout a transmission season, then the value of drugs in eradication programmes would be in no doubt and their efficiency and widespread use would justify heroic measures. But no drug meets these requirements nor would any such one appear to be in sight.

There are a number of papers describing the use of antimalarial drugs in mass treatment, with and without insecticide application. Farinaud and Choumara (1954), working in a hyper-endemic area of Indo-China, found that chloroquine, pyrimethamine or amodiaquine given for two or three months rapidly reduced parasite rates, though the rate subsequently rose and only with amodiaquine did they remain low for several months. Vincke (1954) used pyrimethamine (25 mg weekly for adults) in groups of labourers in the Belgian Congo and he obtained a rapid reduction of the parasite rate which remained low for six months after the drug was withdrawn. Macdonald (loc. cit.) suggests that the persistent effect in Africa, and its absence in Indo-China, may be due to differences in the reaction of strains of the parasite. It is obviously important that the persistent effect of pyrimethamine should be estimated in the countries of Asia for the sporontocidal activities of this drug are of considerable promise in mass chemotherapy.

Turning to the groups difficult to reach, the tribes in mountainous areas, the nomads and migrants and those who are out-of-doors at night, there is a need in Asia for extensive field trials of chloroquinized salt. To Pinotti (1953) goes the credit of being the first to envisage the possibilities of mass treatment by medicating that most common addition to food, table salt. Recently, Coatney *et al.* (1958) have described the preparation of salt medicated with either chloroquine or pyrimethamine. They have shown that the substances are not affected by cooking processes and have tested them with complete success in suppressing *vivax* malaria in a small group of volunteers in Georgia, U. S. A.

Before medicated salt can be introduced in any country, it will be necessary to investigate whether all sources of salt production can be controlled. If small-scale production goes on over a wide area, control may be difficult or even impossible; certainly legal enactments will be necessary to give the required powers.

In addition, the average quantity of salt consumed must be measured so that the dose of drug can be adjusted. Instances are known where mountain people exist with very little salt for many months and then consume large quantities in a short time, when they come in contact with supplies. With pyrimethamine-salt, parasite resistance may be expected and with chloroquine-salt resistance cannot be dismissed as impossible.

In an entirely different category to the above-described situations is the use of drugs in the surveillance stage of malaria eradication programmes, i. e., when malaria transmission has been terminated by residual insecticides and the campaign has been directed towards the discovery of parasite carriers and their complete treatment. In the first stages when cases may be numerous, single-dose treatments, followed by courses of primaquine in *vivax* infections, may be all that is possible. As case treatment becomes increasingly successful, it should then be possible to give the smaller numbers full 3-day treatments. Both regimes, described by Covell, Macdonald and in WHO Technical Reports may need variations to suit local conditions and the described regimes cannot be considered as fixed for all time and all countries.

THE DIFFICULTIES OF DRUG ADMINISTRATION

In a review of the place of drugs in a malaria eradication programme,, the emphasis is on cases of malaria and administration of drugs. In the actual use of drugs the viewpoint changes from cases to men, women and children and from drug administration to swallowing the prescribed number of tablets. The change of viewpoint introduces entirely new problems that are incompletely understood, unpredictable and may even be insoluble.

Firstly, there are the difficulties of discovering parasite-positive cases. No general answer can yet be given to the question, what proportion of malaria cases are found positive in a single thick blood smear? Then again, people whose blood is positive may not feel ill and therefore will not offer a chance of blood examination by seeking treatment.

Should parasitaemia be discovered in a sampling survey, another set of problems arises because it must not be assumed that a man who does not feel sick will take a course of treatment unless obliged to do so; to him it would seem purposeless, still more so if the course consisted of primaquine for fourteen days.

Again, a person may feel ill, may request treatment and may have a blood smear taken, but if his symptoms have disappeared before the blood is examined and the result reported to the treatment unit, the factors described above will again operate.

Formidable as are these difficulties, they are dwarfed by those confronting continuous drug administration. Ray (1948), working with controllable tea estate labourers in India, and taking all possible care to ensure continuous and regular drug administration, found that only 70-80 % of his people never missed a single dose in six months.

Gilroy (1952) in Assam used urine tests to check the administration of proguanil and found that only 56 % of tea estate labourers, said to have been given their tablets, had actually swallowed them. If these difficulties are encountered with disciplined people, accessible and readily supervised, to what extent will they increase when drug administration is applied to village people whase numbers may not be known, who live in distant villages difficult of access and who are, perhaps for the first time, encountering mass chemotherapy?

Why people resist attempts to make them swallow pills week after week is not known. It is quite certainly a complex problem that would justify investigation by experts. The attitude may perhaps be glimpsed if we imagine ourselves lined up outside our houses, or made to visit treatment centres, every week, to swallow a tablet whose purpose is not entirely clear to us and hence is suspect. Health education will certainly help but it is a slow process, perhaps too slow to fit in the time schedule of malaria eradication programmes.

Legal power to enforce drug administration has been suggested. To anyone who is experienced in the lengths to which people will go to evade swallowing medicine and who has seen the growth of consumer-resistance, legal sanction would seem certain to convert guile and indifference into sullen opposition.

CONCLUSIONS

Antimalarial drugs are of unquestionable importance in the surveillance phase of malaria eradication programmes. In limited areas they have effected a rapid though temporary reduction of parasite rates. They may be the method of choice in eradicating malaria in problem groups such as nomads, migrants and dwellers in mountains and forests.

Their theoretical and experimental virtues, however, encounter formidable obstacles in practical application and to underestimate or minimize them does eradication a dis-service and sets the goal further off. Too often it becomes apparent that the greatest hindrance to malaria eradication, and the greatest challenge to the malariologist is, in fact, man himself.

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COMMUNICATION SUR LES OPERATIONS DE DESINSECTISATION ENTREPRISES AU RUANDA-URUNDI

H. Meyus et M. Kivits

Géographie — Le Ruanda-Urundi est situé entre les parallèles 1° 04′ 30″ et 4° 28′ 30″ de latitude sud et entre les méridiens 28° 50′ et 30° 53′ 30″ de longitude est de Greenwich.

Il comprend, au nord, le pays du Ruanda; au sud, celui de l'Urundi.

On distingue quatre régions différentes:

1) Région sise à l'ouest des montagnes formant la dorsale Congo-Nil (Plaine de la Ruzizi et du lac Tanganika). Cette région comprend toute la partie basse, située entre la rivière Ruzizi et le lac Tanganika à l'ouest et la côte 1 100 à l'est.

L'altitude moyenne y est d'environ 850 m.

2) Régions formant la partie de haute altitude, où se trouvent notamment la forêt ainsi que les sommets et les hauts versants de la dorsale Congo-Nil: le pays est très accidenté, il a des altitudes qui varient entre 1 900 et 2 400 m.

3) La région formant ce que l'on peut appeler le plateau central du Ruanda-Urundi:

Il y a dans cette région alternance de collines largement ondulées et de vallées. L'altitude moyenne y est de 1 700 m.

4) Régions des savanes de l'est:

L'altitude mayenne y est d'environ 1 450 m.

Superficie — 52 112 km².

Climatologie:

a) Dans la plaine le climat est tropical:
Température maximale de 33° C — température moyenne de 23° C. Le total annuel des pluies varie entre 800 et 900 mm.

b) Les plateaux du centre ont un climat tempéré: température moyenne de 20°, moyenne maxima de 25° et moyenne minima de 15°. Le total annuel des pluies varie entre 1 200 et 1 300 mm.

c) La crête Congo-Nil a un climat froid et humide: la température moyenne y est de 17,3° C.

d) A l'est du pays, où l'altitude est moindre, la température moyenne est de 22° C. Le total annuel des pluies varie entre 950 mm et 1 100 mm.

En général la saison des pluies s'étend sur deux périodes: du 15 Octobre environ jusqu'au 31 décembre, du 15 Février au 15 Mai.

Il y a une petite saison sèche en Janvier et une grande saison sèche du 15 Mai au 15 Octobre.

Néanmoins , il faut noter que le régime des pluies est excessivement irrégulier, tant par la quantité de précipitations que par leur répartition.

Population et habitations — La population totale du pays compte un peu plus de quatre millions et demi d'habitants (4 517 495). La majorité vit dans des cases.

On distingue trois types de cases:

a) Des cases rondes ayant la forme d'une ruche; leurs parois sont faites en tiges végétales et leur toit est constitué de paille;

b) Des cases cylindriques le plus souvent construites en pisé; leur toit est formé de feuilles de bananiers;

c) Des cases rectangulaires, soit en pisé, soit en roseaux avec un toit de paille.

Certaines cases possèdent des cloisons qui les divisent en plusieurs parties.

Communications -- Il existe un excellent réseau routier et la plupart des chefferies sont aisément accessibles.

Une grande route traverse tout le pays du sud au nord.

Une grande route asphaltée traverse la plaine de la Ruzizi et relie Usumbura à Bukavu.

Le transport du matériel, produits de désinsectisation et du personnel peut de ce fait être réalisé sans dificulté.

Les campagnes de désinsectisation anti-malariennes étendues à tout le territoire furent précédées d'enquêtes et d'opérations partielles.

A) Les opérations de désinsectisation en zone rurale d'altitude moyenne (plaine de la Ruzizi: 850 m) depuis 1952.
B) Les campagnes en région de montagne (territoire d'Astrida: 1 750 m) depuis 1950.
C) Les désinsectisations dans le centre urbain d'Usumbura (850 m) depuis 1950.
D) Les opérations étendues à tout le territoire du R. U. depuis 1956.

A) DANS LA PLAINE

Observations entomologiques:

Le vecteur principal est *Anopheles gambiae*; *Anopheles funestus* intervient pour maintenir l'endémicité malarienne. Les autres anophèles qui y sont observés sont: *pharoensis, coustani, squamosus, marshalli, maculipalpis* et quelques rares *christyi*.

a) *Anopheles gambiae:*

Les gîtes larvaires dans la plaine sont en majeure partie artificiels, crées par l'activité humaine. Les gîtes naturels par contre sont formés par des mares d'eau de pluie, des débordements et des «back-waters» de rivières, plus rarement par des mares et des étangs avc une végétation émergeante et flottante.

Des observations fragmentaires nous portent à croire que dans la majorité des cas, la transmission malarienne se fait par des piqûres à l'intérieur des huttes. Après s'être gorgé, *A. gambiae* va se reposer à l'endroit le plus commode pour lui, endroit qui peut être soit artificiel, soit naturel. Sa préférence semble donc dépendre surtout de facteurs écologiques.

Dans cette région très aride, avant sa mise en valeur, les gîtes possibles étaient peu nombreux et relativement peu protégés.

Maintenant que le facteur humain se développe, les gîtes se multiplient, *A. gambiae* trouve dans les huttes un habitat artificiel qui lui convient très bien.

b) *Anopheles funestus:*

Cette espèce est très fréquente et est le vecteur le plus important après *Anopheles gambiae*. En saison des pluies les rivières sortent de leurs rives et forment des marécages quasi permanents à haute végétation (herbes, roseaux, etc.) donnant l'ombre propice à la prolifération de l'insecte. Les petits ruisseaux (longueur totale 250 km) profonds et peu larges, coulant au milieu de cultures indigènes sont aussi d'excellents gîtes à *A. funestus*. Suite à la grande stabilité de la population d'*A. funestus*, résultant de sa prédilection pour les eaux relativement permanentes, il est le responsable de la continuation des infections en saison sèche. Il est intéressant de noter qu'il est normalement très difficile de trouver des larves d'*A. funestus*, même dans les régions où les adultes abondent dans les habitations.

c) *Anopheles pharoensis:*

Quoique nous n'ayons pas pu établir l'indice sporozoitique, nous sommes portés à croire que cet anophèle n'est pas un vecteur appréciable. En effet, dans la région de Kaharawe cet anophèle abonde tandis que *gambiae* et *funestus* y sont relativement rares. Or l'index plasmodique est de 12 %, alors qu'ailleurs où *pharoensis* est rare, l'index plasmodique est plus élevé. Il se développe uniquement dans les mares d'eau boueuses qui criblent le terrain sablonneux du delta de la Ruzizi.

Les autres anophèles capturée sont: *squamosus, coustani, marshalli, maculipalpis, christyi* et *longipalpis*.

Parasitologie

L'espèce de plasmodium la plus souvent observée est le *Plasmodium falciparum* (96 % des cas). Les autres cas observés sont dûs à *P. vivax*

(2,5 % des cas), à *P. malariae* (0,5 % des cas) et à des formes mixtes *falciparum-vivax* (1 % des cas).

Les travaux de déparasitation s'échelonnent sur les années 1952-57, de 1952 à 1955 ils furent limités à la plaine de la Ruzizi (région I).

a) *Première campagne:*

La campagne débuta en Juillet 1952 et se termina en Septembre 1953, elle comporta deux cycles de traitements:

1er cycle: 16 301 cases indigènes et 3 040 ha de marais.
2ème cycle: 17 731 cases indigènes et 2 165 ha de marais.

b) *Deuxième campagne:* 1954-1956 (3 cycles)

1.er cycle: 18 169 cases indigènes et 2 550 ha de marais.
2ème cycle: 18 611 cases indigènes et 700 ha de marais.
3ème cycle: 19 749 cases indigènes.

Lors de ces trois cycles toutes les cases de la plaine de la Ruzizi ont été dédétisées. En ce qui concerne les marais, ils n'ont été traités qu'une seule fois, pendant la saison sèche, c'est à dire vers la mi-Juillet. La surface d'eau, la seule à traiter, est estimée 1/10ème de la surface totale. Ce traitement a été abondonné en Mars 1955.

c) *Troisième campagne:* 1956

La campagne de désinsectisation de la plaine de la Ruzizi fut englobée dans le programme général de la lutte anti-malarienne s'étendant à tout le territoire du Ruanda-Urundi.

RESULTATS

L'index plasmodique du nourrisson (0 à 1 an) s'établissait à 48,99 % avant la campagne; il a baissé graduellement à 14,63 % après la première campagne, à 12,23 % après la deuxième campagne et à 2,5 % au cours de la troisième campagne.

L'indice plasmodique du total des personnes de tout âge examinées soit 1 601, était avant la première campagne 35,35 %

Après la première campagne il était de 18,41 % sur 3 100 pers. examinées;

Après la troisième campagne de 4,63 % sur 1 079 personnes examinées.

Les possibilités d'infection ont aussi fortement diminué comme le prouve la moyenne des captures d'anophèles par heure, que est passée successivement de 33,28 % à 13,24 % et 0,25. Ceci est confirmé par les indices *gambiae* (I. M. G.) et *funestus* (I. M. F.):

I. M. G.	116,54	avant la campagne.
	69,61	après la première campagne
	21,21	après la deuxième campagne.
I. M. F.	65,95	avant la première campagne.
	22,45	après la première campagne.
	2,02	après la deuxième campagne.

B) EN MONTAGNE

Observations entomologiques:

L'extension du paludisme en région montagneuse est certainement à mettre en rapport avec la mise en valeur d'innombrables et larges vallées marécageuses, jadis incultivables par suite de l'excès d'eau.

On s'est occupé de ce problème depuis 1921. Fin 1932, 10 000 ha avaient été mis en valeur; en 1947, plus de 72 400 ha.

Les cultures en marais s'effectuent en saison sèche, ce qui explique la transmission pendant toute l'année de la malaria en pays montagneux.

Anophèles funestus est le vecteur principal.

Jadin et Fain trouvent à 1 750 m (Astrida) un indice sporozoïtique de 11 % sur 207 dissections.

$$\text{N. B. I. M. G.} = \frac{\text{Nbre A. gambiae X nbre A capturés X 100}}{\text{Nbre A. déterminés X nombre de maisons}}$$

Dans la région de Shangugu (1 800 m) on trouve sur 420 dissections un indice sporozoïtique de 9 %.

Les gîtes les plus favorables au développement des larves sont les drains stagnants herbeux non entretenus où les cypéracées se développent et qui encadrent des lopins de terre cultivés, les bords de rivières herbeuses et les drains à débit régulier.

Tous les adultes capturés le furent dans les cases; ce fait fut d'ailleurs déjà signalé antérieurement par Jadin et Fain.

En altitude, l'*A. funestus* se comporte de la même façon que dans les régions tropicales.

Anophèles gambiae joue également un rôle important dans la dispersion de la malaria en montagne, mais se limite en altitude à un niveau moins élevé que pour *A. funestus.*

Dans le sud-est du pays, à une altitude de 1 100 à 1 250 m le nombre de larves capturées était de 38 % sur 6 250 larves récoltées et pour une période de 10 mois. L'indice sporozoitique était de 10 %.

A Astrida, région plus élevée (1 750-1 800 m) les auteurs Jadin et Fain ne capturent que 0,3 % de *gambiae* sur 4 488 larves, pour une période de 10 mois. Il est certain que l'altitude joue un grand rôle sur la faune anophélienne. Les gîtes favorables aux *gambiae* sont les drains stagnants herbeux, les drains coulants herbeux, flaques d'eau de pluie, etc.

Quoique n'ayont pas entrepris le recherches systématiques sur l'agressivité des femelles *funestus* et *gambiae,* des observations partielles portent à croire que la transmission se fait principalement durant la nuit, à l'intérieur des habitantions.

Notons que, la température à l'intérieur des habitations est sensiblement plus élevée (17 à 20° C) qu'à l'extérieur (15 à 16°).

A. christyi Newstead et Carter:

A. christyi est très répandu en montagne. Les gîtes sont des marais cultivés herbeux, mal entretenus.

Jadin et Fain ont capturé ces anophèles dans les huttes, mais aucun n'a pu déceler des sporozoïtes, sur 54 dissections effectuées.

Reprenant en 1956 l'étude du *christyi* dans la région d'Igenda, à 1 900 m, où cet anophèle est fortement répandu (il représente en effet 80 % de la faune anophélienne), 97 *christyi* furent disséqués sans qu'on ne parvienne à trouver un sporozoïte.

La recherche, par les réactions des précipitines, de l'origine du sang inséré par les anophèles dans la région d'Astrida a montré que *A. christyi* se nourrit principalement de sang bovin.

Les autres anophèles capturés en montagne sont: *coustani Lavoren, dureni, marshalli* Theobald, *demeilloni, garnham, pharoensis, squamosus entebbiensi* Theobald, *ziemanni, mouchetti* Evans, *tenebrosus, implexus.*

Travaux de déparasitation:

Une mission d'étude de désinsectisation a fait des essais de Juillet 1949 à Juin 1950 pour envisager une lutte étendue contre l'anophélisme au Ruanda-Urundi.

Ces essais ont eu lieu en territoire d'Astrida (1 750 à 1 800 m) et ont porté sur une total de 100 000 cases. Les cases ont été traitées avec une concentration de 0,9 g D. D. T. pur/m².

Les marais furent également traités en saison sèche, soit 3 650 ha en Août 1949 et 3 650 ha en Janvier 1950, avec une poudre flottable à 5 % ou à 10 % à raison de 2 g/m².

Ces marais ont été traités parce que les auteurs Vincke, Jadin et plus tard Hocking envisageaient la possibilité d'une transmission en dehors des cases.

A partir de Août 1950, les campagnes se suivirent à des intervalles réguliers (2 g D. D. T. pur/m²). Les résultats de cette dédétisation en zone d'Astrida one été exposés dans un mémoire de l'Institut Royal des Sciences Coloniales [Jadin, Fain, Rupp (3)].

Première campagne: 3 cycles

Cycle 1 — Août 1950-Février 1951: 100 251 cases.

Cycle 2 — Février 1951-Décembre 1951: 79 013 cases et 3 600 ha de marais, traités en Juin.

Cycle 3 — Juillet 1951-Décembre 1951: 100 073 cases et 7 200 ha de marais, traités en Juillet et en Décembre 1951.

Deuxième campagne:

Cycle 1 — Août 1952-Fécrier 1953: 101 414 cases.
Cycle 2 — Février 1953-Août 1953: 104 717 cases et 7 200 ha de marais, traités en Juin et Août 1953.

Troisième campagne:

Cycle 1 — Avril 1954-Octobre 1954: 96 292 cases et 3 600 ha de marais, traités en Juillet.
Cycle 2 — Octobre 1954-Mars 1955: 96 617 cases.
Cycle 3 — Octobre 1955-Mars 1956: 99 743 cases.

Résultats obtenus:

Les résultats obtenus sont des plus encourageants. Avant les essais l'indice plasmodique s'élevait à 51,13 % sur 11 994 examens en goutte épaisse. Pendant la première campagne on relève les indices suivants:

Après le 1er cycle: 24,06 % sur 23 028 examens en goutte épaisse.
Après le 2ème cycle: 13,44 % sur 4 970 g. e.
Après le 3ème cycle: 6,7 % sur 7 500 g. e.

Le premier cycle de la deuxième campagne nous donne 8,7 % sur 5 000 g. e. examinées.

La troisième campagne donne pour les cycles respectifs:

6,6 % sur 3 200 g. e.
6,3 % sur 8 700 g. e.
6,4 % sur 7 300 g. e.

C) EN ZONE URBAINE

A Usumbura, principal centre du Ruanda-Urundi, on peut dire que la paludisme n'est plus un problème de santé.

Le seul danger qui existe encore réside dans le grand nombre de passagers venant des régions où la malaria est endémique et qui restent dans les cités africaines pendant un temps assez long.

Méthodes et mesures adoptées à Usumbura dans la lutte anti-paludique:

1) Lutte anti-larvaire au Centre Urbain et Centre Extra-Coutumier:

La lutte anti-larvaire consiste exclusivement en travaux de drainage, mazoutage des gîtes permanents ou semi-permanents et destruction des gîtes accidentels. Il est certainement prématuré d'affirmer que le contact préalable de l'insecticide avec les larves est indispensable à la réalisation de la résistance. Néanmoins, c'est un problème à ne pas perdre de vue et c'est la raison pour laquelle nous avons préféré l'emploi de mazout et de pétrole.

2) Lutte imagocide:

Nous employons au Centre Extra-Coutumier le H. C. H. à raison de 300 mg d'isomère gamma par m², 3 fois par an.

Bilan actuel de la lutte anti-paludique:

Indice plasmodique des nourrissons

1950			
1951			
1952	7,7 %	1 382	G. E.
1953	2,1 %	2 905	»
1954	4,8 %	4 115	»
1955	2,2 %	6 268	»
1956	1,9 %	7 725	»
1957	1,3 %	14 726	»

Avant la dédétisation l'indice plasmodique chez le nourrisson était de 31,2 %; actuellement le même indice est de 1,3 %.

D) CAMPAGNE GENERALISEE

En raison des bons résultats obtenus dans ces zones pilotes, le Service Médical décida d'étendre le programme de désinsectisation à tout le pays jusqu'à la côte 2 000 m.

Les opérations de désinsectisation sont exécutées dans les villes et les grands postes par les équipes des services d'hygiène publique, tandis que dans les zones rurales les opérations ont été confiées par adjudication à une firme privée.

Au total, 224 équipes de désinsectisation sont en activité sur l'ensemble du Territoire.

L'étendue de la zone soumise aux opérations est de 40 000 km². Toutes les parois intérieures des locaux habités ou fréquentés par les habitants subissent deux fois par an une pulvérisation d'une suspension aqueuse de D. D. T., à raison de 2 g de D. D. T. technique par mètre carré. Une première campagne de désinsectisation s'est faite de Juin 1956 à Janvier 1957, tandis qu'une seconde campagne commencée en Janvier 1957, s'est terminée en Octobre.

Le nombre total des habitations traitées est de 921 552, soit 913 146 en zones rurales et 8 406 dans les villes.

Ces maisons ont subi au total 1 137 759 pulvérisations d'insecticide au cours de l'année et la surface traitée est de 40 068 180 m². On compte en moyenne 30 m² de surface traitée par habitation rurale et 300 m² pour une maison de ville.

Le nombre d'habitants protégés directement par les désinsectisations est de 4 100 000, tandis que 400 000 personnes résidant sur les hauts plateaux sont indirectement protégées du fait que ces plateaux sont complètement entourés de régions traitées.

Le coût total des opérations pour une campagne de pulvérisations s'élève à à10 850 000 Frs congolais, soit 9 400 000 Frs (217 000$ U. S. A.) pour 4 036 254 habitants des zones rurales et 1 450 000 Frs pour 63 746 habitants des villes. Le prix de revient par personne protégée est de 2,32 Frs (± 5 cents U. S. A.) dans les zones rurales et de 22,66 Frs (45 cents U. S. A.) dans les zones urbaines.

Cette différence de 1 à 10 correspond à l'étendue des surfaces à traiter (30 m² en moyenne par maison rurale et 300 m² par maison de ville).

A raison de deux campagnes par année, le prix de revient de la lutte antipaludique serait donc de 4,64 Frs par an (10 cents U. S. A.) et par habitant dans les zones rurales et de 45 Frs (90 cents U. S. A.) dans les villes.

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HEPATOMEGALIE ET PALUDISME CHEZ L'ENFANT AFRICAIN

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Au cours d'examens cliniques systématiques chez les enfants africains du Moyen-Congo, en vue de rechercher les signes de carence protidique et en particulier de dépister le kwashiorkor, nous avons été frappé par la fréquence des hépatomégalies qui, dans certaines régions, se rencontrent chez 50 pour 100 des enfants.

Il s'agit toujours de gros foies mous, indolores, atteignant et parfois dépassant l'ombilic. Cette hépatomégalie est fréquente chez l'enfant de 5 à 12 ans; elle diminue progressivement pendant l'adolescence et disparaît chez l'adulte.

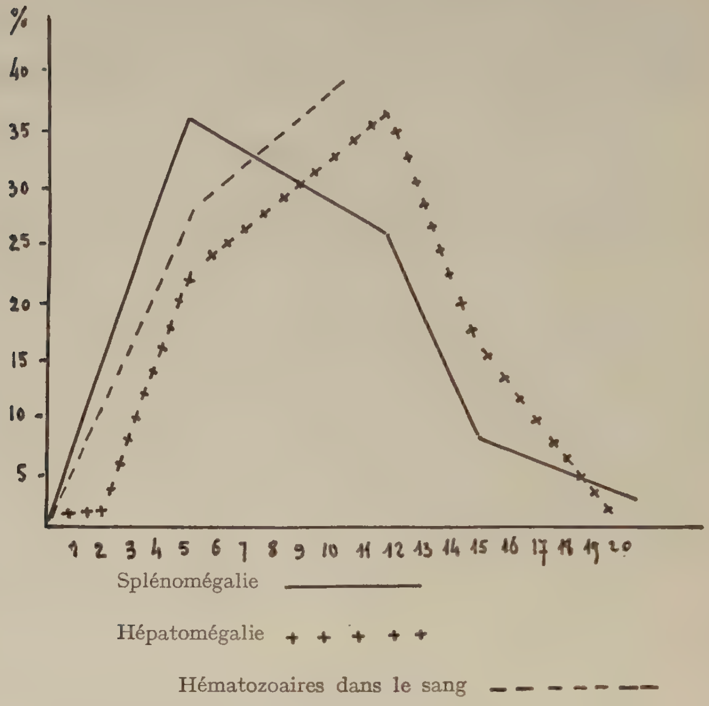
Nous avons d'abord été tenté de rattacher cette hépatomégalie au kwashiorkor, mais, d'une part, elle ne s'accompagnait d'aucun signe de malnutrition protidique, et, d'autre part, elle se rencontrait dans les régions où les enquêtes alimentaires montrent que la ration protidique est suffisante. Ainsi, au Moyen-Congo, dans la région forestière de Mossendjo, où le taux des hépatomégalies atteint 35 pour 100, une enquête sur l'alimentation de 92 familles suivies pendant une semaine a montré que la ration protidique était inférieure de 5 pour 100 à la ration standard préconisée par le National Research Council, différence négligeable, d'autant plus que l'apport en protéïne animale était suffisant. Il nous était dès lors difficile d'expliquer ces gros foies, par une carence protidique, qu'il s'agisse de carence d'apport ou d'utilisation.

Par ailleurs, la bilharziose vésicale ou intestinale est inconnue dans la région et ne peut être rendue responsable de ces hépatomégalies.

C'est alors qu'en comparant la fréquence des hépatomégalies et des splénomégalies, nous avons été frappé par la similitude des courbes en fonction de l'âge.

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 759-764, 1959

Graphique 1 — Mossendjo — Enfants: 4 202



Sur le graphique ci-dessus, on a porté en abcisse l'âge des sujets et en ordonnée le taux de splénomégalies, le taux d'hépatomégalies et le taux d'infestation du sang par l'hématozoaire. (Recherche d'hématozoaire sur goutte épaisse).

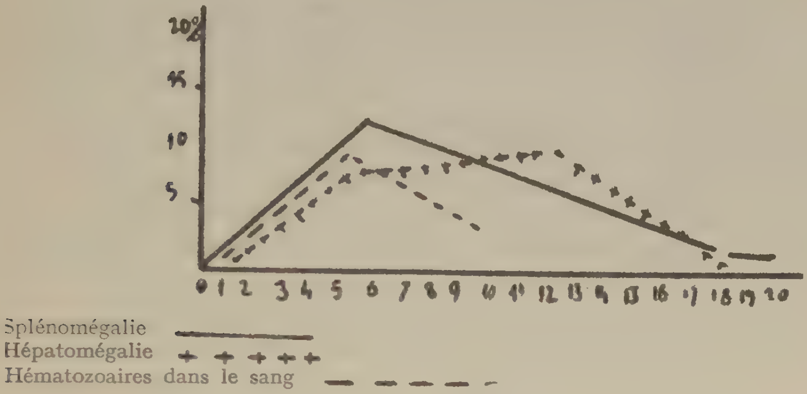
L'examen a porté sur 5 632 sujets habitant une région forestière du Moyen-Congo à forte endémicité palustre.

Sur ce graphique, les trois courbes ont la même forme et atteignent progressivement les mêmes chiffres:

36 pour 100 pour les splénomégalies
38 pour 100 pour le taux d'infestation palustre
35 pour 100 pour les hépatomégalies.

Le maximum des splénomégalies se situe à 5 ans, celui de l'infestation du sang par l'hématozoaire à 10 ans et celui des hépatomégalies à 12 ans. L'hépatomégalie est donc décalée dans le temps par rapport aux splénomégalies; elle apparaît plus tard et disparaît plus tard. Chez l'adulte, on ne retrouve plus que 3 pour 100 d'hépatomégalie et 4 pour 100 de splénomégalies.

Graphique 2 — Brazzaville — Enfants: 2 577



Le graphique 2 concerne un quartier de Brazzaville où l'endémicité palustre est faible en raison de la lutte imagocide.

L'examen a porté sur 5 799 sujets dont 2 577 enfants.

Là encore, les courbes ont la même forme, mais sont légèrement décalées dans le temps. A 5 ans, le taux des splénomégalies atteint 12 p. 100 et celui des hématozoaires dans le sang 7 p. 100; à 12 ans le taux des hépatomégalies est à 10 p. 100. L'hépatomégalie apparaît et disparaît après la splénomégalie.

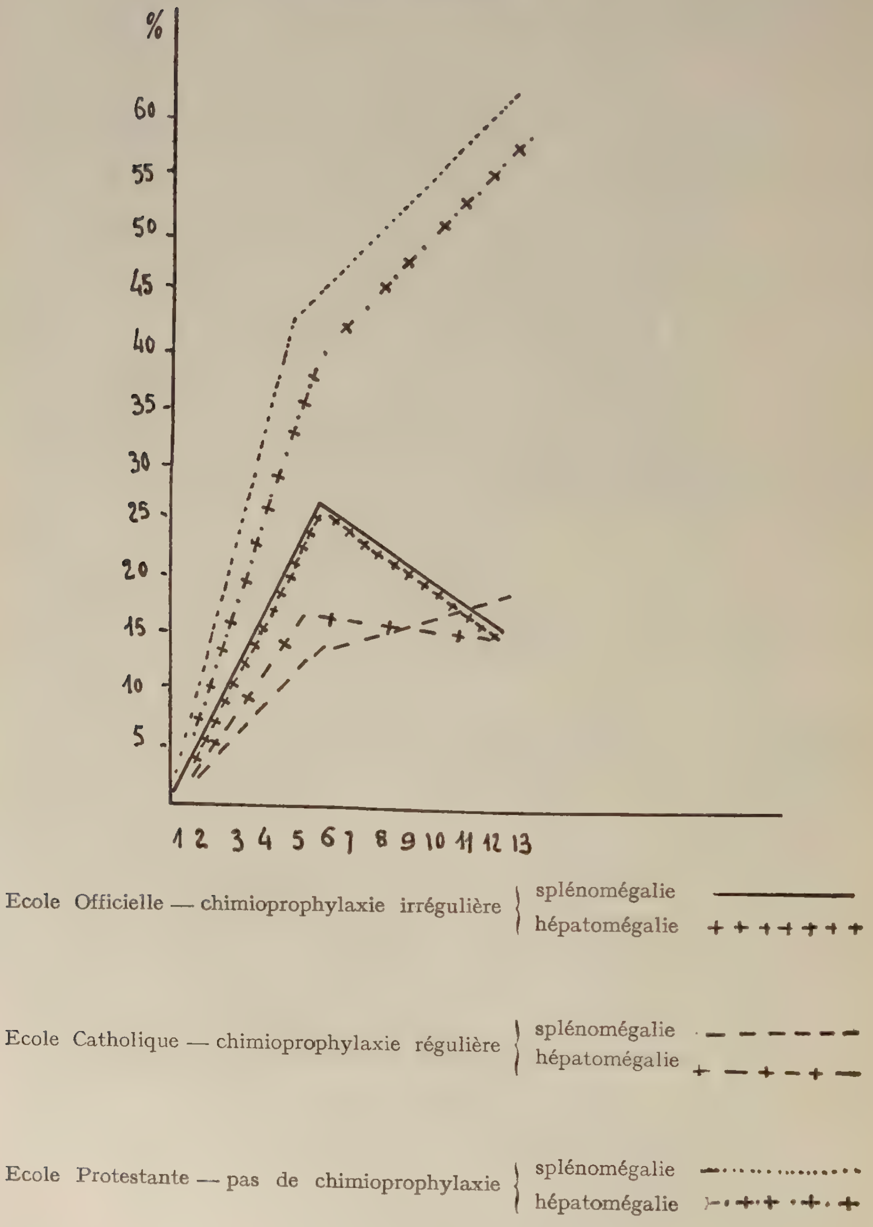
La comparaison des graphiques 1 et 2 nous montre que la courbe des hépatomégalies suit fidèlement celle des splénomégalies, qui est elle-même liée à l'infestation palustre.

Le graphique 3 représente le taux de splénomégalies et d'hépatomégalies chez les enfants d'un même centre, ayant par conséquent les mêmes conditions de vie, entre autres la même nourriture et les mêmes risques d'infestation palustre.

L'examen a porté sur 605 enfants âgés de 1 à 12 ans répartis entre trois écoles et garderies d'enfants; l'école officielle 240 élèves, la mission catholique 235 élèves, la mission protestante 130 élèves.

Graphique 3 — Ouesso

Ecole Officielle: 240 — Ecole Catholique: 235
Ecole Protestante: 130



Les enfants de l'école officielle suivaient irrégulièrement une chimioprophylaxie palustre par la nivaquine. Ceux de l'école catholique suivaient une chimioprophylaxie régulière. Quant à ceux de l'école protestante, ils n'en suivaient aucune.

La courbe des splénomégalies reflète fidèlement cette différence de chimioprophylaxie entre les écoles. Mais nous voyons que l'hépatomégalie obéit non moins fidèlement aux mêmes règles.

Nous avons vu que la malnutrition protidique ne saurait être rendue responsable de ces hépatomégalies, pas plus d'ailleurs que la bilharziose que n'existe pas dans cette région.

Evoluant parallèlement aux splénomégalies palustres, obéissant comme elles à la chimioprophylaxie, il nous paraît logique de rattacher ces hépatomégalies au paludisme. Ces enfants, avant de constituer leur immunité, font une hyperplasie massive de tout leur système réticulo-endothélial. Le foie et la rate, organes particulièrement riches, participent côte à côte à ce processus.

A cette hyperplasie du tissu réticulo-endothélial correspond une importante augmentation des γ globulines et des eu-γ globulines dans le sérum des sujets examinés.

Les électrophorèses et les fiches réticulo-endothéliales exécutées par le pharmacien commandant Bergot, de l'Institut Pasteur de Brazzaville, sur 100 sérums à Brazzaville et sur 125 sérums à Mossendjo donnent les résultats moyens suivants:

1° — *Diagrammes électrophoretiques*

	Albumine	Globulines			
		α^1	α^2	β	γ
Sérum Brazzaville	44	6	9	15	26
Sérum Mossendjo	40	6	7	11	36

2° — *Fiches réticulo-endothéliales*

	PH final	7,5	7	6,6	6,3	5,7	5,1	4,7	4,4
Sérum Brazzaville	Lecture	20	27	40	58	90	70	40	15
Sérum Mossendjo	Lecture	30	42	70	90	114	72	45	17

En comparant les résultats de Mossendjo à ceux de Brazzaville, nous voyons que le taux des γ globulines et des eu-γ globulines est nettement plus élevé à Mossendjo qu'à Brazzaville. Cette écart correspond à celui des hépato-splénomégalies. Il est le reflet fidèle de la réaction du tissu réticulo-endothélial et traduit la différence de gravité de l'endémie palustre entre les deux régions.

Ces gros foies, de même que ces grosses rates, disparaissent chez l'adulte. Que le foie conserve les stigmates histologiques de cette hyperactivité temporaire, c'est possible et même probable. Les anatomopathologistes ont mis en évidence dans le foie palustre une majoration progressive du précollagène hépatique, terrain favorable au développement ultérieur des cirrhoses de l'adulte.

En conclusion, les hépatomégalies que nous avons rencontrées chez l'enfant noir du Moyen-Congo ne sont pas dues à la malnutrition ou à la bilharziose. Leur étiologie la plus probable est le paludisme, car la courbe de ces hépatomégalies suit fidèlement celle des splénomégalies, elle obéit comme elle à la chimioprophylaxie palustre et disparaît chez l'adulte.

RÉSUMÉ

Au cours d'examens systématiques portant sur 12 000 sujets, l'auteur a été frappé par la fréquence de l'hépatomégalie chez l'enfant africain au Moyen-Congo. Cette hépatomégalie ne peut-être expliquée, ni par la malnutrition protidique ni par les bilharzioses, qui sont inconnues dans les régions prospectées.

En établissant des graphiques en fonction de l'âge, il a constaté la similitude des courbes de ces hépatomégalies avec celles des splénomégalies et de l'infestation palustre.

Par ailleurs, les hépatomégalies obéissent comme les splénomégalies à la chimioprophylaxie palustre. Il rattache donc ces hépatomégalies au paludisme. Les hépato-splénomégalies palustres traduisent l'hyperplasie du tissu réticulo-endothélial, qui se manifeste biologiquement par une augmentation importante des globulines, comme l'ont montré les analyses effectuées sur 225 sérums.

L'ANOPHELISME ET LA SENSIBILITE DES ANOPHELES VECTEURS AUX INSECTICIDES REMANENTS EN ROUMANIE

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L'étude sur l'anophélisme et surtout celle des vecteurs du paludisme a formé l'objet d'une sérieuse préoccupation depuis plus de 40 ans en Roumanie, considérée dans le passé parmi les pays à paludisme endémique.

Les investigations effectuées dans les zones à conditions orohydrographiques favorables au développement de l'anophélisme, ont été poursuives pendant certaines années le long des bassins des rivières jusqu'à des altitudes où les rares cas enregistrés, appartenaient au paludisme importé. On a identifié en Roumanie, à part les anophèles non-transmetteurs (*A. claviger, A. plumbeus* et *A. hyrcanus pseudopictus*) les vecteurs suivants du paludisme: *A. maculipennis typicus* et *messeae, A. labranchiae atroparvus* et *A. sacharovi.* Chacun de ces quatre vecteurs à aire caractéristique de répartition, a joué un rôle différent dans la transmission de la maladie.

Ainsi, *A. m. typicus,* vecteur du paludisme des zones des plateaux de la Moldavie et des zones des colines du reste du pays, ne peut plus transmettre la maladie dans les conditions climatiques de notre pays, au delà de 300-350 m d'altitude, où nous le rencontrons dans une proportion de 100 %. *A. m. messeae,* vecteur important dans la zone inondable du Danube et des grandes rivières, ainsi que dans les rizières, entretenant pendant certaines périodes le paludisme à caractère grave, est dépassé en importance par *A. labranchiae atroparvus,* rencontré tant dans la zone du littoral que dans les zones intérieures à terrain salé et eaux stagnantes légèrement saumâtres. *A. sacharovi,* espèce très anthro-

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pophile dans notre pays, limité à une zone qui commence à la frontière sud de la Dobroudgea et continue vers le nord, le long du lac Raselm jusqu'au Delta du Danube.

La présence d'*A. sacharovi* a largement contribué au caractère grave du paludisme, qui a atteint en 1945-1946 (District de Tulcea) un degré de holoendémie.

Des travaux limités d'assainissement ont atteint dans une faible mesure le vaste système hydrographique favorable au développment de la faune anophélienne. L'attaque massive sur l'anophélisme, presque non-modifié, revient à l'action des insecticides rémanents, appliqués après une préalable expérience au laboratoire et sur le terrain. Les caractéristiques biologiques, l'inter et la péridomesticité des anophèles vecteurs «ont imposé pendant la première étape, 1949-1950, l'emploi (répété chaque année) sur une vaste échelle de la méthode imagicide intégrale aux insecticides de type rémanent, comme méthode cantitative de lutte antipaludique, en vue d'interrompre la transmission» (Ciuca *et coll.* 1957).

Les produits employés comme imagicides dans la lutte antianophélienne ont été le D. D. T. (approximativement 2 g/m^2 et le H. C. H. (approximativement 0,25-0,37 g isomère gamma/m^2). On a procédé de même à la lutte antilarvaire au H. C. H. cristaux, 0,0025-0,0030 g isomère gamma/m^2 et double dose sur des zones limitées: les chantiers de Giurgiu (1952-1953) et la vallée de Cara-Su (1954-1955).

Les opérations imagicides, dirigées par rapport aux données phénologiques, commençaient 10-15 jours avant l'apparition en masse de la première génération des anophèles, qui se produit vers le 8-20 mai dans les régions de plaine du Danube, la Dobroudgea, la vallée inférieure du Pruth et dans le Banat, et de 10-15 jours plus tard sur le littoral et le nord de la Moldavie.

La durée de la rémanence des insecticides — dans nos conditions de travail — macro et microclimat, type d'habitation et support, formules des insecticides, dosage — est de 6 mois en moyenne pour le D. D. T., 2 g/m^2 et de 2 ½-3 mois pour le H. C. H. 0,25-0,37 g isomère gamma m^2. Les anophèles en Roumanie hivernent à l'exception de *A. labranchiae atroparvus* qui est semi-hibernant. La période de transmission varie de 4 à 5 mois, pendant laquelle se succèdent 5 à 7 générations. Pour réaliser l'interruption de la transmission par une seule aspersion annuelle, on commençait généralement à traiter les habitations par le D. D. T., à plus longue rémanence. On a rarement traité une localité deux fois de suite au cours de la même année.

En ce qui concerne la lutte antilarvaire, celle-ci se répétait en rapport avec les indications entomologiques, avant l'apparrition des larves du IV^{ème} stade avancé et des nymphes, moins sensibles aux insecticides.

Les résultats obtenus dès les premières années, la baisse considérable du paludisme, ont permis de modifier les méthodes employées. On a procédé à la rationalisation des aspersions en fonction de la morbidité paludéenne et de l'intensité du potentiel anophélien. On a suspendu progressivement les traitments de certaines localités, la protection antianophélienne se continuant par l'aspersion des «foyers» et des «barrières insecticides». Il existe toutefois des zones où la méthode imagicide intégrale a été employée pendant 8-10 années consécutives.

En connaissant le phénomène de «résistance acquise» chez les insectes pour certains produits toxiques, surtout pour les insecticides rémanents — *M. domestica* (Suède 1946, Italie, Grèce, 1947)) et spécialement *A. sacharovi* (Grèce, 1951) — l'attention des investigateurs s'est concentrée dès le début sur l'éventuelle apparition de ce phénomène chez les vecteurs du paludisme.

Les contrôles effectuées annuellement: sur la densité anophélienne dans les localités traitées, les tests des anophèles introduits dans les cages d'intoxication aux panneaux (Simmons) et le test d'endémicité, ont été les méthodes utilisées sur le terrain, parallèlement aux investigations de laboratoire et intoxications expérimentales des générations successives de l'espèce *A. labr. atroparvus* (Ardelean I. et Cristescu A., 1951).

Aux méthodes déjà énumérées, on a ajouté dès 1956 le test Busvine-Nash, test adopté par tous les pays qui poursuivent des investigations sur la sensibilité ou sur la résistance des anophèles aux insecticides dans le cadre des recherches coordonnées par l'Organisation Mondiale de la Santé, et dans une moindre mesure, les microtests (l'application topique dorsale sur le thorax d'insecticides). Les tests (méthode Busvine-Nash) sur 22 569 anophèles (traiatés + témoins) capturés de 36 localités en 1956 et de 40 738 anophèles (traités + témoins) capturés de 25 localités en 1957, ont été effectués surtout dans les localités où les aspersions ont été interrompues ou bien n'avaient jamais été effectuées. Dans les localités traitées, le nombre réduit d'anophèles capturés provenait presque exclusivement des nouvelles habitations ou des habitations non-traitées.

Les résultats obtenus en 1957, confirment ceux de l'année 1956, avec quelques données en plus quant à la variation de la sensibilité des anoprèles.

Les indices de mortalité (au D. D. T. et H. C. H.) ne diffèrent pas trop dans les localités pulvérisées — maximum dix années — de ceux des localités où les pulvérisations ont été suspendues les trois dernières années. A l'appui de ces résultats qui indiquent le maintien de la sensibilité des anophèles provenant des localités pulvérisées d'une manière suivie, viennent aussi les données de la densité réduite, enregistrée pendant les périodes du maximum de développement des moustiques, 1 ½--2 mois à partir du traitement aux insecticides — de même que l'absence des cas de paludisme (Eforia, Murighiol, Sarulesti, Ciulinesti, etc.).

On a pu tester mensuellement les anophèles des localités qui n'ont jamais été traitées aux insecticides aussi bien que celles où les aspersions ont été interrompues les trois dernières années. Les variations de sensibilité ainsi enregistrées sont déterminées par des facteurs outre les insecticides.

Ces tests ont montré une sensibilité plus prononcée des anophèles mâles, comparativement aux femelles.

On a noté de même, une variation saisonnière de la sensibilité anophélienne aux insecticides: Les anophèles testés en Avril 1957 représentés par des générations résiduelles étaient très sensibles (Podgorii, Iassy, avec prédominance du *A. m. typicus*). Les anophèles testés en Juin, Juillet, Août et même Septembre, ont présenté une sensibilité accentuée qui diminuait en Octobre dans la plaine du Danube et sur le littoral. Par exemple dans la localité Creata-Lesile, non-traitée, à anophélisme représenté par *A. messeae* 51,4 %, *A. m. typicus* 23,2 % et *A. labr. atroparvus* 25,3 % on a enregistré du 12 Juillet au lo Septembre 1957 pour le D. D. T. 2,0 %: indices de mortalité de 48,0 % à 79,7 %; pour le D. D. T. 4,0 % de 92,2 % à 100 %, tandis que pour les témoins l'indice de mortalité était de 0,6 % à 14,5 %. Pour les épreuves effectuées le 28 Octobre 1957 (baisse brusque de la température) aux anophèles non-gorgés et au corps gras, on a enregistré des valeurs moindres: pour le D. D. T. 2,0 %: indice de mortalité 26,0 %, pour le D. D. T. 4,0 %, indice de mortalité 68,0 %, tandis que pour les témoins 0. Cette baisse de la sensibilité aux insecticides a été signalée en 1956 pour *A. maculipennis* en Iran et en Roumanie; il paraît que la variation de la sensibilité pendant certaines périodes «est causée par les changements physiologiques qui se produisent chez les moustiques au début de l'hibernation» (Zulueta, 1956) et notamment le développement en masse du corps adipeux, alors que l'activité ovarienne cesse. La baisse de la sensibilité en automne dans le nord de la Moldavie (Podgorii, 1957) a commencé plus tôt, le mois de Septembre.

La diminution de la sensibilité pour les insecticides a également été enregistrée le mois d'Octobre 1957 sur le littoral où *A. sacharovi* a été présent dans la faune anophèlienne à un taux de 27,7 % Agigea, et 78,9 % Enisala.

D'ailleurs *A. sacharovi* paraît être une espèce plus sensible à une série de facteurs, tels le traumatisme, température, insecticide. Ce fait a été signalé en 1955 lors des recherches effectuées sur le littoral par la détermination des femeles d'après les caractères des «ovipositions obtenues par la dissection» (Sandulesco M., Marotinesco St.) méthode qui a permis l'identification des anophèles moribonds et morts récemment. Tandis que dans la formule anophélienne de la localité d'Agigea établie par détermination des ovipositions obtenues normalement, *A. sacharovi* se trouvait á un taux de 33,0 %, selon les caractères des ovipositions par dissection, le taux était de 79,5 %.

L'augmentation du degré de tolérance à l'insecticide pendant la pré--hibernation (Sept. ou Oct.) a été plus grande pour Lindan et Dieldrine comparativement au D. D. T. (tableau 1). Ainsi prenant comme exemple les données obtenues par les doses supérieures, il résulte que lorsque dans la localité d'Agigea le taux de la mortalité baisse de 63,3 % (Août) à 10,0 % (Oct.) pour le D. D. T. 2,0 % et de 100 % (Août) à 57,1 % (Oct.) pour le D. D. T. 4,0 %; au Lindane la baisse est beaucoup plus prononcée pour 0,04 % de 96,0 % (Août) à 0 (Oct.) et pour 0,08 %: de 100 % (Août) à 4,5 % (Oct.). Dans la localité de Podgorii (Nord de la Moldavie) pour Dieldrine 0,2 %: baisse de 80,0 % (Août) à 1,6 % (Sept.) et pour 0,4 %: de 97,5 % (Août) à 9,8 % (Septembre).

Pendant l'époque active des anophèles en Roumanie, le maximum de sensibilité enregistrée était de Juin à Septembre (1957) sur le littoral et la plaine du Danube, tandis qu'au nord du pays, où l'hibernation commence plus tôt, le maximum de la sensibilité était en Juin et Août.

Un autre facteur qui a exercé une influence sur la sensibilité des anophèles, au cours de nos expériences, est la température. Ainsi, le mois d'Août (mois chaud), pour les deux lots d'anophèles testés dans les mêmes conditions, la température variant de 3-6° C, pendant l'expo-

Tableau 1 — *La variation saisonnière de la sensibilité des anophèles au D. D. T., H. C. H.-gamma et Dieldrine par la méthode Busvine-Nash*

Localité	Agigea				Podgorii			
Espèce	*A. labr. atroparvus* 68,7 % *A. sacharovi* 27,7 % *A. m. typicus* 1,6 % *A. m. messeae* 1,9 %				*A. m. typicus* 96,9 % *A. labr. atroparvus* 3,0 %			
Date des essais	31.8.1957		17.10.1957		14-21.8.1957		25-27.9.1957	
Température pendant l'exposition	24°C		16-17°C		27°C		24°C	
Température pendant les 24 heures suivantes, min. et max.	17-25°C		13-16,5°C		26-28°C		21-24°C	
Anophèles testés	Nombre testés	Mortalité non corrigée %	Nombre testés	Mortalité non corrigée %	Nombre testés	Mortalité non corrigée %	Nombre testés	Mortalité non corrigée %
D. D. T. 0,5 %	60	11,6	20	0	—	—	—	—
D. D. T. 1,0 %	60	16,6	20	0	202	4,9	—	—
D. D. T. 2,0 %	60	63,3	20	10,0	205	33,2	102	24,5
D. D. T. 4,0 %	60	100	21	57,1	—	—	100	69,9
HCH-gamma 0,01 %	50	18,0	27	0	—	—	—	—
HCH-gamma 0,02 %	50	70,0	27	0	188	44,6	55	6,1
HCH-gamma 0,04 %	50	96,0	27	0	187	91,7	105	13,3
HCH-gamma 0,08 %	50	100	22	4,5	—	—	—	—
Dieldrine 0,2 %	—	—	—	—	40	80.0	60	1,6
Dieldrine 0,4 %	—	—	—	—	40	97,5	51	9.8
Témoins	120	1,6	20	0	104	10,6	—	—

sition à l'insecticide dans l'étable ou en plein air, on a obtenu des taux différents de mortalité, notamment, plus élevés pour les lots maintenus à des températures plus élevés. (tableau 2).

Les résultats des microtests effectués sur 7 774 anophèles capturés dans la nature, viennent à l'appui des données obtenus par la méthode Busvine-Nash en démontrant le maintien de la sensibilité des anophèles aux insecticides plusieurs années de suite dans les localités traitées et l'augmentation du degré de tolérance au cours de la pré-hibernation.

Observations sur les anophèles d'élevage — Malgré les déficiences de nos élevages, des 3 784 tests effectués sur les anophèles (méthode Busvine--Nash) et 70 (microtests) il ressort:

a) Les anophèles d'élevage paraissent parfois présenter une sensibilité un peu plus grande que ceux capturés dans la nature; *b*) les anophèles des générations F_1 descendants des captures effectuées dans les localités traitées 8 à 10 années de suite, des localités où l'aspersion avait été suspendue les trois dernières années et les localités qui n'avaient jamais été pulvérisées, ne présentaient pas de différences nettes de sensibilité; *c*) l'absence de la variation saisonnière de la sensibilité des anophèles d'élevage fait ressortir l'influence des facteurs de milieu qui déterminent la variation de la sensibilité dans la nature; *d*) les échantillons capturés sur le terrain ont présenté parfois des individus qui toléraient de grandes doses d'insecticides; leur descendants dans certains cas ont présenté une sensibilité similaire à celle des échantillons capturés sur le terrain, d'autrefois, une sensibilité plus réduite.

RÉSUMÉ ET CONCLUSIONS

Les vecteurs du paludisme en Roumanie, *A. m. typicus*, *A. m. messeae*, *A. labr. atroparvus* et *A. sacharovi* ont une période d'activité à partir du printemps jusqu'à l'automne, assurée par la succession de 5 à 7 générations. La durée de la transmission du paludisme dans les différentes zones varie de quatre à cinq mois.

En tenant compte des caractéristiques biologiques, oecologiques et phénologiques des vecteurs locaux, ainsi que de la durée de la rémanence 6 mois en moyenne pour le DDT, 2 gr/m² et de 2 1/2-3 mois pour le HCH, 0,25-0,30 gr. isomère gramma/m² au cours du programme de lutte antipaludique, on a employé des insecticides surtout comme imagicides; la séries des pulvérisations a commencé avec le DDT à rémanence plus longue. Une seule aspersion annuelle assurait l'interruption de la transmission dans la majorité des localités.

TABLEAU 2 — *Variation de sensibilité des anophèles par rapport à la température du temps d'exposition à l'insecticide D. D. T.*

Localité	Date	Température		Nombre de anophèles traités au DDT en huile Risella — %				Témoins	Mortalité — % DDT en huile Risella — %				Témoins
		Pendant l'exposition	Pendant 24 h.	0,5	1,0	2,0	4,0		0,5	1,0	2,0	4,0	
Saftica *n*	14/VIII/1957	29-35,5°C	23-21,5°C	114	114	100	123	113	14,0	28,9	59,0	93,8	8,8
» *a*	»	26-30°C	»	116	114	110	108	101	12,0	21,9	44,6	81,5	6,9
Creata *n*	9/VIII/1957	28-31°C	23,5-29°C	111	120	100	100	108	9,9	34,2	73,0	100	5,5
Lesile *a*		24-25°C	»	116	100	100	103	107	9,5	18,0	48,0	92,2	4,7

n = en nature
a = dans les étables

Le contrôle des localités traitées 8-10 années de suite, les localités où le traitement a été suspendu les 3 dernières années et celles qui n'ont jamais été traitées, la détermination de la densité anophélienne, l'appréciation de la rémanence de l'insecticide, le test de la sensibilité aux insecticides par la méthode Busvine-Nash, ainsi que le test d'endémicité, ont montré:

Les anophèles des localités traitées aux insecticides pendant plusieures années de suite (maximum 10 années) n'ont pas acquis une résistance aux insecticides DDT et HCH gamma, résistance qui permette la présence d'un nombre d'anophèles capables de transmettre le paludisme. Cette observation est également confirmée par la densité très réduite notée 1 1/2 mois après la pulvérisation et par l'absence de cas de paludisme.

Les variations de sensibilité apparaissent tant dans les localités traitées que dans les non-traitées. Elles ne peuvent donc pas être dues à l'influence des insecticides et paraissent plutôt appartenir à une variation de la sensibilité naturelle, déterminée par une série de facteurs, tels, le sexe, l'état physiologique en rapport avec les saisons et avec les variations de température enregistrées pendant l'exposition aux insecticides.

Le maintien de la sensibilité des anophèles vecteurs locaux aux insecticides rémanents utilisés, permet dans notre pays de continuer à employer la méthode imagicide, moyen nécessaire et précieux dans le complexe des mesures préconisées pour l'éradication du paludisme.

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A BRIEF SUMMARY ON MALARIA ERADICATION CAMPAIGN HELD IN TURKEY

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Malaria Control Campaign in Turkey has started in the year of 1925 and due to the proper use of insecticides, spleen indices have almost resched zero in regions where malaria was highly endemic. Consequently, investigations were made by Prof. A. Corradetti, the well known WHO malaria consultant, in the country, to change malaria control campaign into malaria eradication. Thus, the organization was recognized in line with his recommendations. Furthermore, a survey was made for the establishment of infant parasite index in 1956 which lead to divide the country into the following three malaria groups of regions.

1. Group A — Covering Central Plateau, Black Sea and Eastern mountains where there was transmission up to an altitude of 1 000 meters. In this group of regions, attacking phase of malaria eradication program was applied in 1957 and now consolidation phase is operated in 1958 where transmission was completely interrupted in this groups of regions except two foci in which muçh is being done for its elimination.

2. Group B — Covers Western Anatolia, Marmara and Aegean coasts where it was found out that transmission was still present up to an altitude of 1 200 meters. In this group of regions, attacking phase of the program shall continue for two years.

3. Group C — Covers South and South Eeastern Anatolis where transmission was identified up to 1 500 meters and in this group of regions attacking phase shall last for three years.

A part of personnel in A group of regions were transferred to B and C groups of regions in 1958 in order to strengthen the activies. On the other hand, surveillance organization in all of these groups of regions is regularly and carefully proceeding in case finding. However, following the application of D. D. T. 75 % wettable powder as 2 g/m^2 on surfaces in B and C groups of regions, epidemiological investigations were made by J. de Zuluela in Adana region and it was found out that *A. sachorovi,* the most important vector in Turkey, has gained a high resistance against D. D. T. and a high tolerance of LC 50 = 2,60 and LC 50 = 1,75 in Antalya and Balikesir regions respectively. As there were 2 093 malaria cases by the end of June 1958 in Adana region, D. D. T. was replace with Dieldrin and a thorough application with Dieldrin has been already made in this region. On the other hand, *A. superpictus,* the other important vector in Turkey, is susceptible to both D. D. T. and Dieldrin. As malaria cases were increasing in the summer months of 1958 in South Eeast, the susceptitbility testing team, at present, is working in that part of the country.

In the attacking phase of the program held in 1957, 1 128 tons os D. D. T. 75 % wettable powder was used in 16 929 villages of A, B and C groups of regions. Furthermore, 99 764 blood examinations were made out of suspected cases through the surveillance organization in the second six months of the same year and 4 355 of them were found as positive cases. Of these 3 764 were *P. vivax,* 527 were *P. falciparum,* 31 were *P. malariae,* 23 were mixed and 10 unidentified. In the first six months of 1958, 539 886 blood examinations were made out of suspected cases and 2 231 of them were found positive cases. They were, 2 093 *P. vivax,* 65 *P. falciparum,* 65 *P. malariae* and 8 mixed. In addition, two different parasitic indices from 1 to 5 years old children and babies less than 1 year old infants are regularly made in the country.

At present malaria eradication campaign is regularly and properly continuing in the country with 100 chiefs of sectional offices, 34 chiefs of regional offices and 12 chiefs of surveillance groups of regions, all medical doctors, trained in malariology and 1 625 malaria sanitarians and 41 laboratory technicians as technical staff.

Our main difficulties are resistance problems, moving population and temporary dwellings, case findings and their pertaining treatments.

We are indebted very much to the staff of WHO and UNICEF for their close cooperation and support they give for the cause of the aim. And, much of our gratitude goes to Prof. Corradetti and Dr. Zulueta.

THE INFLUENCE OF MALARIA CONTROL ON VITAL STATISTICS IN CEYLON [1]

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D. P. H., M. D. B. S. (Lond.), F. R. C. P. (Edin),
L. M. S. (Cey.), F. R. S. H.

INTRODUCTION

Ceylon is a small island which is 25,332 square miles in extent, and lies between 5° 55′ and 9° 50′ north latitude and 79° 42′ and 81° 53′ east longitude. It is 270 miles at its greatest length and 140 miles at its greatest breadth.

The present capital of the country is Colombo situated on the western coast of the island. One of the ancient capitals was Anuradhapura situated in the north central area. This city was devasted by a pestilence in 300 A. D. It would appear from the «Mahavansa» one of the oldest chronicles of Ceylon history that this pestilence was probably malaria.

From 1 300 A. D. onwards the indigenous medical literature describes a fever which manifests daily, every other day or every fourth day. Anorexia, chill, rigor, gooseskin, headache and loss of consciousness are described as further symptoms associated with this fever.

Ribeiro in his History of «Ceileo» (1640) Cordiner (1807) and Tenant (1860) make references to a fever that is identifiable as malaria. It would appear, therefore, that malaria has been endemic for several centuries. To what extent it was really prevalent is not known.

Since 1906 authentic information is available about the incidence of malaria and epidemics have been recorded every 4-6 years. The last epidemic was in 1945-46.

One of the worst epidemics was in 1934-35 when over four million people were affected and about 50,000 people died of the disease in a space of a few months.

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[1] Published in *The Journal of Tropical Medicine and Hygiene*, vol. LXI.

Proc. 6th Int. Congr. Trop. Med. and Malar., 7: 776-792, 1959

Climatic zones

For epidemiological studies of malaria Ceylon is divided into three climatic zones. (Rustomjee, 1944). These three zones are called Dry, Intermediate and Wet, and are shown in map. 1. The Dry Zone constitutes the North-Eastern sector of the island. Malaria was hyperendemic in this zone and the spleen rate was over 60 %. The major portion of the island falls within this zone (vide map. 2).

The South-Western sector of the Island forms the Wet Zone and it is free from malaria. About one fourth of the country falls within this zone and the spleen rate was below 10 %.

The area in between these two zones is known as the Intermediate Zone. The spleen rate in this area was between 20-40 % and this zone was subjected to epidemic malaria.

Incidence of malaria

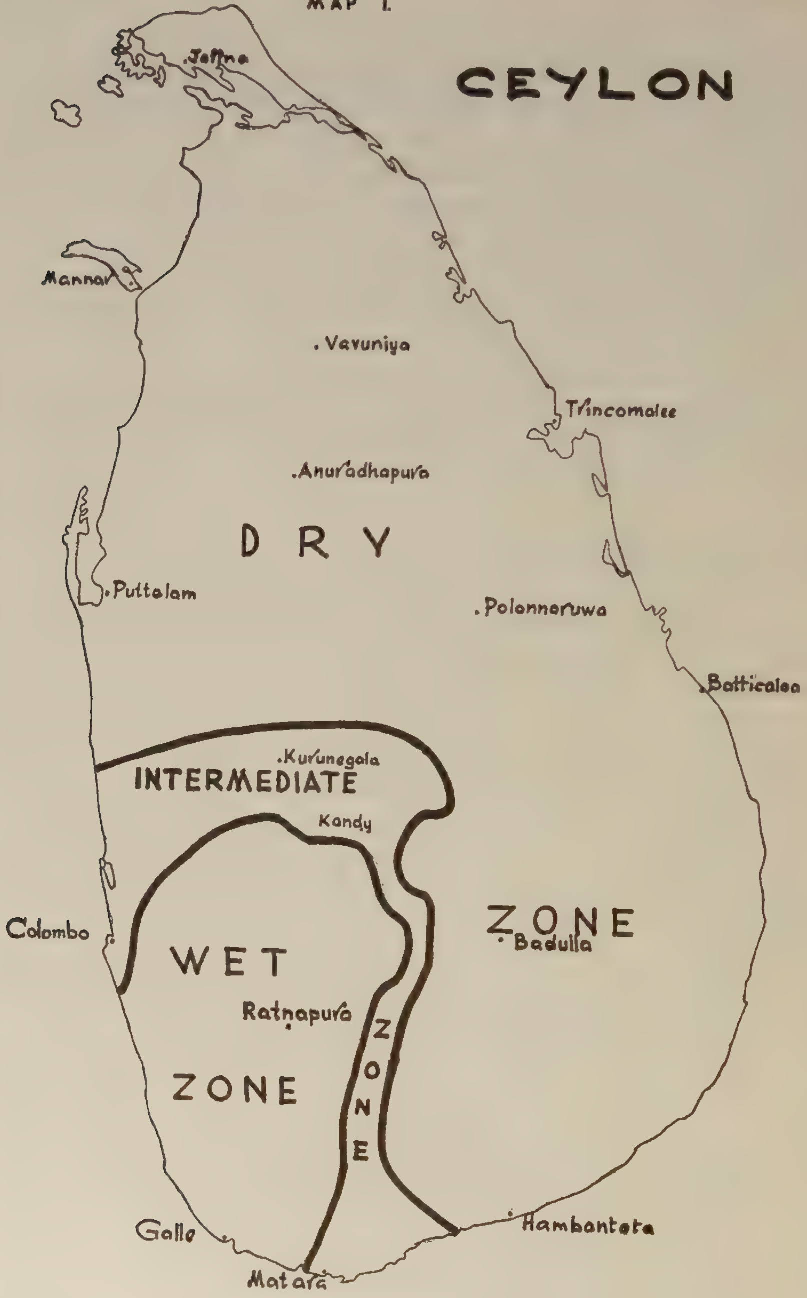
A considerable degree of morbidity occurred in the island due to malaria. The number of cases of malaria and the rate per 1 000 population by five year intervals from 1935 to 1945 and then by years up to 1956 are shown in table 1. In 1935 there were nearly 5 ½ million cases and the rate was 974 per 1 000 of the population. This was an epidemic year for malaria and consequently the number of cases was very high; and in other years the rate was about 400 per 1 000. There is a marked reduction in the incidence of the disease from 1947. The rate per 1 000 has come down from 413 in 1946 to 0.35 in 1956. This reduction is the result of residual spraying with D. D. T.

Table 2 shows the spleen rates from 1939-1955. As with the incidence of malaria from about 1947 the spleen rates also show a marked decline from 11.8 in 1946 to 0.2 in 1955.

MALARIA CONTROL

Organised State intervention in the control of Malaria dates back to 1921 when a Malarialogist was appointed. In 1927 a Special Division was set up to carry out this work. This Division was assisted by a

MAP I.


CEYLON
Jaffna
Mannar
Vavuniya
Trincomalee
Anuradhapura
DRY
Puttalam
Polonnaruwa
Batticaloa
Kurunegala
INTERMEDIATE
Kandy
ZONE
Badulla
Colombo
WET
Ratnapura
ZONE
ZONE
Galle
Hambantota
Matara

MAP II

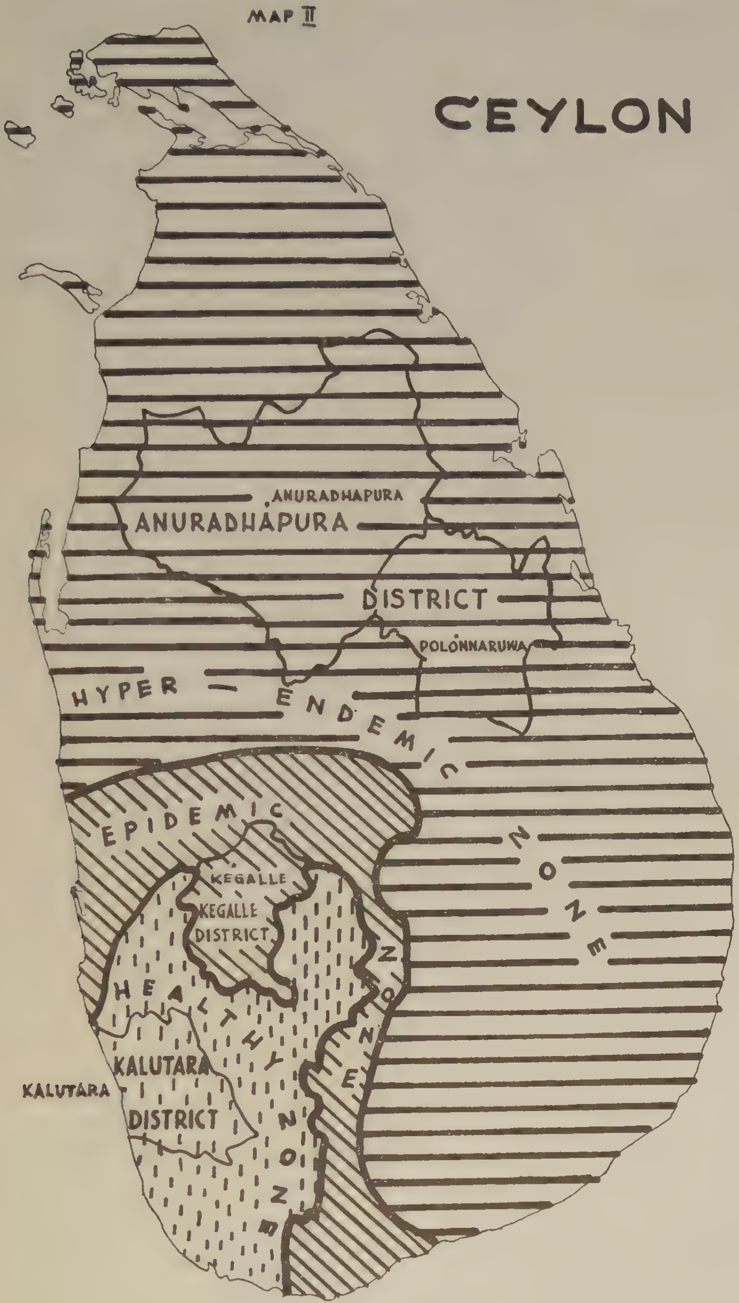

CEYLON
ANURADHAPURA
ANURADHAPURA
DISTRICT
POLONNARUWA
HYPER — ENDEMIC ZONE
EPIDEMIC ZONE
KEGALLE
KEGALLE DISTRICT
HEALTHY ZONE
KALUTARA
KALUTARA DISTRICT

TABLE 1 — *Malaria morbidity and mortality — Ceylon — 1935-1956*

Year	Estimated population	Morbidity		Mortality	
		No. of cases	Rate per thousand	No. of deaths	Rate per million
1935	5,608,000	5,459,539	974	47,326	8,439
1940	5,951,000	3,413,618	674	9,169	1,532
1945	6,496,000	2,539,949	391	8,539	1,310
1946	6,695.000	2,768,385	413	12,587	1,873
1947	6,879,000	1,459,880	212	4,562	661
1948	7,100,000	775,276	109	3,349	471
1949	7,297,000	727,769	100	2,403	328
1950	7,547,000	610,781	81	1,901	252
1951	7,743,000	448,100	58	1,599	206
1952	7,942,000	269,024	34	1,049	132
1953	8,098,000	91,990	11	722	89
1954	8,385,000	29,656	3.5	447	53
1955	8,589,000	7,317	0.85	268	31
1956	9,165,000	7,186	0,35	144	16

TABLE 2 — *Spleen rate by years*

Year	Rate
1940	17.9
1941	18.4
1946	11.8
1947	10.3
1948	5.8
1949	2.7
1950	1.2
1951	0.8
1952	0.6
1953	0.3
1954	0.3
1955	0.2

Sanitary Engineer and a Medical Entomologist. The chief control measures were antilarval work such as oiling, Paris-greening, use of larvivorous fish, drainage and filling.

After the epidemic of 1934-1935 the malaria control work was extended specially to deal with epidemic malaria. The measures previously adopted for the control of this disease were intensified and in addition pyrethrum insecticide sprays were used against the adult mosquito. Suppresive drug therapy was also carried out. The results achieved by these control measures were very limited.

The discovery of D. D. T. as a potent residual insecticide and the demonstration of its successful use in the control of malaria during World War II gave the lead to Ceylon to become the first country in the East to inaugurate a scheme of malaria control by indoor spraying of residual insecticides. The first mobile unit for spraying was established in November 1945. This proved effective and the residual spraying was extended in 1946 to cover all malarial and potentially malarial areas throughout the country. Thus both epidemic and endemic areas were covered by the spraying programme. Spraying of all houses with D. D. T. or B. H. C. was done every six weeks. Later the period was extended to 3 months and the dosage per application was 50-60 mgm per square foot.

To detect breeding places of *A. culicifacies,* the only vector in Ceylon, investigations were carried out continuously.

In 1955 residual spraying was interrupted in all parts that were regularly sprayed, except where transmission was known to exist. At the same time a system of Vigilance Units and sub-units were set up for blood filming of all fever cases, and for the investigation and treatment of all positive cases of malaria. As a result of these control measures, in 1957 there were only 6,999 clinical cases of malaria and 6,811 with positive laboratory findings.

It has now been decided to launch an eradication programme by carrying out intensive residual spraying for a short period associated with detection and treatment of all cases.

Registration of vital statistics

Civil registration of births, marriages and deaths has been practised in Ceylon since 1867, and there is therefore a well established tradition of vital statistics. In recent years a very high standard of completeness of registration has been attained and, with the proviso that in rural areas there is occasionally failure to register either the birth or the death of babies who die in the first few days of life, the problem of under-registration can for all practical purposes be ignored. A detailed discussion of the problem will be found in Raja Indra (1955).

To complement the information derived from vital registration, population censuses were taken at 10 year intervals from 1871 to 1931 and, more relevant to the present discussion, in 1946 and 1953. Even the most recent census figures suffer both from misstatements of age and under-enumeration of the youngest age groups. The problem is discussed in the successive census reports and in Sarkar (1957), which contains an extensive bibliography of the demography of the island. In the present study no attempt has been made to alter figures published in the Census Reports for 1946 and 1953.

Effect on vital statistics

Malaria Control has had a marked influence on the vital statistics of Ceylon. Table 3 shows the Birth, Death, Maternal and Infant Mortality Rates, by five year intervals from 1931 to 1947 and then by years to 1956. It will be noted that since 1947, after the commencement of residual spraying with insecticides, there has been a steady and marked decline in all the death rates. This influence will be discussed in subsequent paragraphs.

TABLE 3 — *Vital statistics*

Year	Birth rate	Death rate	Maternal d. rate	Infant d. rate
1931	37.0	22.1	20.8	158
1936	34.0	21.8	21.6	166
1941	36.4	18.8	15.3	129
1946	38.2	20.3	15.5	141
1947	39.3	14.3	10.6	101
1948	40.5	13.2	8.3	92
1949	39.8	12.6	6.5	87
1950	40.4	12.6	5.6	82
1951	40.5	12.9	5.8	82
1952	39.5	12.0	5.8	78
1953	39.4	10.9	5.0	71
1954	36.2	10.4	4.6	72
1955	37.9	11.0	4.1	71
1956	36.4	9.8	3.8	67

The selected areas

To study the effect of Malaria Control on vital statistics three districts in the three climatic Zones were selected, namely, Anuradhapura in the Dry Zone, Kurunegala in the Intermediate Zone and Kalutara in the Wet Zone. The location of those districts are shown in map 2. A district is an administrative division and the island is divided into 22 such districts.

The incidence of malaria and the spleen and parasite rates for these three selected districts are shown in tables 4, 5 and 6 respectively. These are shown separately in tabular form for a better understanding of the discussion on the influence that malaria control has exercised on the vital statistics of the Island.

TABLE 4 — *Number of malaria cases*

Year	Anuradhapura	Kegalle	Kalutara
1950	58,531	20,382	19,065
1951	39,794	16,555	16,051
1952	19,889	7,418	10,546
1953	8,078	1,288	734
1954	828	120	276
1955	555	5	45

TABLE 5 — *Spleen rates*

Year	Anuradhapura	Kegalle	Kalutara
1941	76.6	11.6	2.2
1942 to 1946	Not done	Not done	Not done
1947	36.9	4.0	0.3
1948	18.3	2.9	0.2
1949	7.1	1.1	0.01
1950	3.4	0.6	0.0
1951	1.9	0.16	0.0
1952	0.9	0.08	0.8
1953	0.2	0.1	0.08
1954	0.2	0.4	0.2
1955	0.4	0.3	0.02

TABLE 6 — *Parasite rates*

Year	Anuradhapura	Kegalle	Kalutara
1946	3.6	3.3	0.7
1947	2.7	1.2	0.0
1948	1.8	0.2	0.0
1949	0.8	0.1	0.0
1950	0.1	0.0	0.0
1951	0.4	0.0	0.0
1952	0.5	0.0	0.0
1953	0.5	0.0	0.0
1954	0.0	0.0	0.0
1955	0.0	0.0	0.0

The spleen and parasite rates for Anuradhapura, in the hyper-endemic Zone, was much higher than in the other two Districts in 1946. However, by 1954 the rates are almost the same for the three districts. The Vital statistics data examined here relate principally to these three administrative districts selected as representing typically different ecologies with respect to the incidence of malaria at the earlier period. The figures for each area have been studied for two periods. The earlier period 1945/7 shows the situation on the eve of the intensive spraying programme. The second period 1952/4 mirrors largely the results of that programme. Each period represents a census year and the years on either side of it. In computing age-specific death rates, the population for the census year has been used, since inter-censal estimates at present available are of doubtful efficiency and are in any case extremely difficult to make, since the success of the Anti-Malaria Campaign, by permitting the opening up of large areas of secondary jungle, has resulted in extensive internal movements of population.

One administrative point regarding the figures requires mention. On 1st October, 1953 a new district (Polonnaruwa) was created, largely by division of the Anuradhapura district. The District Revenue Office of Tamankaduwapalata was taken out of the old Anuradhapura district and combined with seven villages from the former Matale district (not considered here) to form a new district. About 89 % of the population enumerated at the 1953 census in this new area came from Tamankaduwapalata; and, in presenting figures for Anuradhapura district for 1954, the whole of the new Polonnaruwa district has been included.

The result has been a overstatement of the number of deaths in 1954 and the understatement of the population by approximately 7,400, out of a total of a little over 229,000.

Other influences

In comparing vital statistics for areas which were formerly malarial with other areas it must be borne in mind that the removal of hyperendemic malaria has had secondary social and economic results. The Anuradhapura district, in particular, has been the scene of extensive pioneering schemes which have involved a considerable influx of population, both permitting and demanding improved medical and transport facilities. Some of the improvements in the health of the population may, therefore, be attributable to these secondary effects as well as to the actual control of malaria. But such progress is one and indivisible and no atttempt is made here to separate out the effects.

Effect on death rates

The most obvious and dramatic effect is in the reduction of the death rate at all ages in the malarial district in relation to the non--malarial. Table 7 shows age-specific deaths at the two periods for each of the three districts.

It is evident from the table that, compared with the improvement over the same period in Kalutara, there has been a dramatic reduction in the death rates at all ages in Anuradhapura district. In the period 1945/7 age-specific death rates in Anuradhapura were from 2-3 times the corresponding rates in Kalutara. By 1952/4 this situation no longer obtained and some rates were actually lower in Anuradhapura. In Kegalle the initial discrepancy was not so great but a similar relative improvement can be observed.

Whilst a relatively greater fall in the death rates in malarial areas is noticeable at all ages, particular interest attaches to the infant and maternal mortality rates. Table 8 shows the historical series of infant mortality rates for the three selected areas for the period 1944/56. The rates being independent of census information it is of course possible

TABLE 7 — *Mean death rates 1945-7 and 1952-4 for 3 selected areas*

Age groups	Anaradhapura		Kegalle		Kalutara	
	45/7	52/4	45/7	52/4	45/7	52/4
0-4	100.1	30.8	52.8	31.1	43.1	25.8
5-9	7.4	2.4	7.0	3.3	5.8	3.5
10-14	5.2	1.4	2.4	1.0	2.6	1.1
15-19	11.2	3.2	3.5	1.5	3.3	1.3
20-24	15.3	2.7	6.1	2.2	5.8	2.3
25-29 30-34	15.5	3.4	6.6	3.3	6.7	2.8
35-39 40-44	19.8	4.1	8.1	3.8	6.9	3.4
45-49 50-54	28.9	7.0	11.7	5.7	9.8	5.6
55-59 60-64	48.7	13.3	21.3	12.3	19.3	13.4
65 and over	117.5	58.8	91.3	68.5	88.0	69.6
Total	26.4	9.8	16.5	10.0	14.7	9.4

to extend them beyond the censal years. The fall in the infant mortality rates of Anuradhapura district during the six years 1945/50 probably represents a phenomenon unparalleled elsewhere.

Whilst the total enumeration of births and deaths in Ceylon reaches a high standard the recording of causes of death still leaves much to be desired. In rural areas covering a very large part of the island, certification of death is through lay registrars and, unless the deceased person was the subject of an inquest, or died in hospital, the cause of death rests entirely on lay statements. This being so, little confidence can be attached to maternal mortality rates for rural areas, since these depend upon locating a cause of death to complications of pregnancy, child birth and puerperium as classified in items 640-689 of the International Classification of Deaths, Injuries and Causes of Deaths.

Even where the cause of death is acurately recorded the maternal mortality rate fails to take into account deaths which result from the greater lethality of diseases such as malaria, when contracted by women whose resistence is undermined by frequent and closely spaced pregnancies. As a yardstick, therefore, of the improved maternal death rates in areas formerly malarial, table 9 shows separately for the two

TABLE 8 — *Infant mortality rates per 1000 live births for selected areas 1944-1956*

	1944	1945	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955	1956
Anuradhapura[1]	317	272	207	150	102	90	74	69	81	73	68	71	66
Kegalle	102	127	124	83	75	75	72	70	72	67	75	70	67
Kalutara	92	92	90	92	77	74	68	70	67	48	55	59	54
All Ceylon	135	140	141	101	92	87	82	82	78	71	72	71	67

[1] Boundary changed after 1953. See text.

TABLE 9 — *Specific death rates per 100,000 population at age 15-44 by sex for selected areas — 1945-7 & 1952-4*

	1945/7	1952/4	1952/4 rate as % of 1945/7
Anuradhapura			
Males	1149.5	249.2	21.7
Females	2234.0	475.2	21.3
Male rate as % of Female	51.5	52.4	
Kegalle			
Males	497.0	198.3	39.9
Females	1928.5	357.0	18.5
Male rate as % of Female	25.8	55.5	
Kalutara			
Males	501.2	209.0	41.7
Females	661.1	303.2	45.9
Male rate as % of Female	75.8	68.9	

sexes the age-specific death rates per 100,000 population computed by relating all deaths among persons aged 15-44 to the Census population at these ages.

This procedure discloses a remarkable difference between the three areas. In Anuradhapura the 1945/7 death rates were extremely high for both sexes, though the rate for females in this group was practically double the male rate. Proportionate improvement following the Anti-Malaria Campaign has been similar for both sexes although of course the absolute reduction in the female death rate has been far greater. In the Kegalle District a completely different pattern presents itself. In 1945/7 the female death rate was nearly three times the male, and was comparable to that in Anuradhapura, whereas the male death rate was approximately the same as that in Kalutara. In the Kegalle District a proportionately far great reduction has taken place in the female death rate, and it is interesting to note that the absolute reduction is nearly of the same order of magnitude as that experienced in Anuradhapura.

Table 10 shows the birth rate in women, aged 15-44, for the two periods and in the three areas under review. Again the differences are striking. Their interpretation is however complicated. Still births are

TABLE 10 — *Mean annual birth rates per 1000 women aged 15-44 for selected areas — 1945-7 & 1952-4*

	1945/7	1952/4
Anuradhapura	190.7	246.1
Kegalle	155.7	185.1
Kalutara	154.3	150.4

only registered in a limited number of urban areas in Ceylon and the birth rates are not, therefore, available for the complete districts here studied. Earlier foetal deaths were not recorded anywhere. The figures for live births classified by age of the mother have only been available since 1952.

An increase in the live-births rate, even when related to women aged 15-44, may reflect changes in the age composition of the female population, changes in the extent of foetal loss, or changes in the absolute fertility rate (i. e. in the rate of conception). Available information does not, therefore, suffice fully to elucidate what effect the control of malaria has had on different factors, effecting the rate of increase of the population.

Nevertheless it appears probable that all three forces have been operative though in what proportion it cannot be determined. Table 11 shows the available data for Anuradhapura district, where the change

TABLE 11 — *Female population and live births Anuradhapura district* 1946 and 1953

Age	Population				Live births			
	1946		1953		1946		1953	
	Number	%	Number	%	Number	Rate per 1000	Number	Rate per 1000
15-19	5 898	21.2	8 136	18.7	—	—	1 311	161.1
20-24	6 299	22.6	10 890	25.0	—	—	3 626	333.0
25-29	5 521	19.9	9 401	21.6	—	—	2 907	309.2
30-34	3 845	13.8	5 527	12.7	—	—	1 380	249.7
35-39	3 848	13.8	6 062	13.9	—	—	923	152.3
40-44	2 402	8.6	3 481	8.0	—	—	112	32.2
Total	27 813	100	43 497	100	5 482	197.1	10 259	235.9

has been greatest. In fact it will be seen that the internal age structure of the female population aged 15-44, has changed relatively little. If the female population in 1953 had been distributed by age exactly as it was in 1946 with the same (1953) age-specific birth rates, the overall rate would have been 229.3 instead of the actual 235.9, a trivial difference.

It may be assumed, therefore, that the difference between the birth rates of 197 per 1 000 and 229 per 1 000 represents a change between the two years which is independent of shifts in age composition. The gain of 32 on 229 births represents a rate of 140 per 1 000. Whilst there can be little doubt that foetal loss has diminished with other deaths as a concequence of malaria control, this figure seems to be too high to be attributed to that cause alone, and we may assume, therefore, that pari passu with the death rate there may well have been an increase in fertility.

SUMMARY

Ceylon had been severely affected by malaria for centuries past, and a greater part of the country was subject to hyper-endemic malaria, whilst some other parts were subject to epidemic malaria, a smaller portion only being healthy.

The influence of Malaria Control in a hyper-endemic district, a district subject to epidemic malaria, and a healthy district has been discussed.

The registration of vital statistics in the country is considered sufficiently reliable for the purpose of the study.

A dramatic reduction of the death rates in all age groups in the malarial areas has been recorded. Such a reduction has not occurred in the healthy area. The rates in the malarial areas have reached the levels obtaining in healthy areas.

The fall in the infant mortality during the six years 1945-50 in the hyper-endemic area is probably unparalleled elsewhere.

Similar reductions have been recorded among deaths in females of the child bearing age.

Malaria Control also appears to have contributed, amongst other causes, to an increase in fertility.

ACKNOWLEDGEMENT

I am indeed thankful to Dr. R. Padley, W. H. O. Consultant in Statistics, and the late Dr. L. F. Gunaratne, Superintendent, Anti-Malaria Campaign, in Ceylon for their valuable advice, guidance and assistance in the preparation of this paper.

ABSTRACT OF THE PAPER ON «THE INFLUENCE OF MALARIA CONTROL ON VITAL STATISTICS IN CEYLON»

For several centuries Malaria appears to have been endemic in Ceylon. Authentic records of its occurrence in epidemic form, every four or six years, is available from 1946. For the epidemiological study of Malaria the island is divided into three climatic zones; Dry, Intermediate and Wet.

A severe epidemic occurred in the island in 1934/35 affecting over four million people with about 50,000 deaths. The incidence of the disease up to 1945 was about 400 per thousand of the population.

Measures for the control of the disease have been adopted on a organised scale since 1921. Residual spraying with D. D. T. and B. H. C. was started in 1946. Since then there has been a marked reduction in the incidence of the disease and the rate now is 0.35 per thousand population.

To demonstrate the influence of Malaria control on the vital statistics the changes that have resulted in the vital statistics in 3 districts, tistics the changes that have resulted in the vital statistics in 3 districts one from each of the three climatic zones have been discussed. The registration of vital statistics in the country is considered sufficiently reliable for the purpose of such a study.

A dramatic reduction of the death rates in all age-groups in the malarial area have been recorded, and these have reached the levels obtaining in healthy areas. The fall in the infant mortality rate during the 6 years 1945 to 1950 in the hyperendemic area is probably unparalleled elsewhere.

Similar reduction have been recorded among deaths in females of the childbearing age. Malaria control also appears to have contributed amongst other causes to an increase in fertility.

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